ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTES OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Austria	Bayer Austria GmbH Herbststraße 6-10 1160 Wien Austria	Ciproxin	250 mg	film-coated tablets	oral use	250 mg
		Ciproxin	500 mg	film-coated tablets	oral use	500 mg
		Ciproxin	750 mg	film-coated tablets	oral use	750 mg
		Ciproxin	100 mg/50 ml	solution for infusion	intravenous use	2 mg/ml
		Ciproxin	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciproxin	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
		Ciprofloxacine « BAYER »	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciprofloxacine « BAYER	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
		Ciproxin	5 %	oral suspension	oral use	5 %
		Ciproxin	10 %	oral suspension	oral use	10 %
Belgium	BAYER SA-NV Avenue Louise 143 Louizalaan 143 B - 1050 Bruxelles-Brussel Belgium	Ciproxine	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciproxine	100 mg/50 ml	solution for infusion	intravenous use	2 mg/ml
		Ciproxine	100 mg	film-coated tablets	oral use	100 mg
		Ciproxine	250 mg	film-coated tablets	oral use	250 mg
		Ciproxine	500 mg	film-coated tablets	oral use	500 mg
		Ciproxine	750 mg	film-coated tablets	oral use	750 mg
		Ciproxine	5 g/100 ml	oral suspension	oral use	50 mg/ml
		Ciproxine	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciproxine	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
Bulgaria	Bayer HealthCare AG D-51368 Leverkusen Germany	Ciprobay	250 mg	film-coated tablets	oral use	250 mg
		Ciprobay	500 mg	film-coated tablets	oral use	500 mg
		Ciprobay	200 mg /100 ml	solution for infusion	intravenous use	2 mg/ml

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
		Ciprobay	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
		Ciprobay XR	500 mg	modified release tablets	oral use	500 mg
Cyprus	BAYER HELLAS ABEE, Greece 18-20 Sorou Street, 15125 Marousi, Athens, Greece	Ciproxin	250 mg	film-coated tablets	oral use	250 mg
		Ciproxin	500 mg	film-coated tablets	oral use	500 mg
		Ciproxin	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
Czech Republic	Bayer HealthCare AG D-51368 Leverkusen Germany	Ciprobay	100 mg/50 ml	solution for infusion	intravenous use	2 mg/ml
		Ciprobay	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciprobay	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
		Ciprobay Uro	100 mg	film-coated tablets	oral use	100 mg
		Ciprobay	250 mg	film-coated tablets	oral use	250 mg
		Ciprobay	500 mg	film-coated tablets	oral use	500 mg
		Ciprobay	750 mg	film-coated tablets	oral use	750 mg
Denmark	Bayer HealthCare AG D-51368 Leverkusen Germany	Ciproxin	250 mg	film-coated tablets	oral use	250 mg
		Ciproxin	500 mg	film-coated tablets	oral use	500 mg
		Ciproxin	750 mg	film-coated tablets	oral use	750 mg
		Ciproxin	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciproxin	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
		Ciproxin	50 mg/ml	oral suspension	oral use	50 mg/ml
		Ciproxin	100 mg/ml	oral suspension	oral use	100 mg/ml
Estonia	Bayer HealthCare AG D-51368 Leverkusen	Ciproxin	250 mg	film-coated tablets	oral use	250 mg
		Ciproxin	500 mg	film-coated tablets	oral use	500 mg

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
	Germany	Ciproxin	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciproxin	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
Finland	Bayer HealthCare AG 51368 Leverkusen, Germany	Ciproxin	250 mg	film-coated tablets	oral use	250 mg
		Ciproxin	500 mg	film-coated tablets	oral use	500 mg
		Ciproxin	750 mg	film-coated tablets	oral use	750 mg
		Ciproxin	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciproxin	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
France	Bayer Santé 13, rue Jean Jaurès 92807 Puteaux Cedex France	Ciflox	250 mg	film-coated tablets	oral use	250 mg
		Ciflox	500 mg	film-coated tablets	oral use	500 mg
		Uniflox	500 mg	film-coated tablets	oral use	500 mg
		Ciflox	750 mg	film-coated tablets	oral use	750 mg
		Ciflox	250 mg/5 ml	oral suspension	oral use	50 mg/ml
		Ciflox	500 mg/5 ml	oral suspension	oral use	100 mg/ml
		Ciflox	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciflox	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
Germany	Bayer Vital GmbH D-51368 Leverkusen Germany	CIPROBAY	100 mg/50 ml	solution for infusion	intravenous use	2 mg/ml
		CIPROBAY	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		CIPROBAY	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
		CIPROBAY URO	100 mg	film-coated tablets	oral use	100 mg
		CIPROBAY	250 mg	film-coated tablets	oral use	250 mg
		CIPROBAY	500 mg	film-coated tablets	oral use	500 mg
		CIPROBAY	750 mg	film-coated tablets	oral use	750 mg
		CIPROBAY	5 g/100 ml	oral suspension	oral use	50 mg/ml
		CIPROBAY	10 g/100 ml	oral suspension	oral use	100 mg/ml
	Bayer Healthcare AG D-51368 Leverkusen, Germany	Ciprofloxacin ANTIBAC	250 mg	film-coated tablets	oral use	250 mg
		Ciprofloxacin ANTIBAC	500 mg	film-coated tablets	oral use	500 mg

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
		Ciprofloxacin ANTIBAC	750 mg	film-coated tablets	oral use	750 mg
		Ciprofloxacin ANTIBAC	100 mg/50 ml	solution for infusion	intravenous use	2 mg/ml
		Ciprofloxacin ANTIBAC	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciprofloxacin ANTIBAC	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
		Ciprofloxacin BAYER	100 mg/50 ml	solution for infusion	intravenous use	2 mg/ml
		Ciprofloxacin BAYER	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciprofloxacin BAYER	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
		Ciprofloxacin VITAL	100 mg/50 ml	solution for infusion	intravenous use	2 mg/ml
		Ciprofloxacin VITAL	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciprofloxacin VITAL	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
Greece	BAYER HELLAS ABEE 18-20 Sorou Street 15125 Marousi , Athens, Greece	CIPROXIN	100 mg/50 ml	solution for infusion	intravenous use	2 mg/ml
		CIPROXIN	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		CIPROXIN	400 mg/200 ml	solution for infusion	intravenous use	2 mg / ml
		CIPROXIN	500 mg	film-coated tablets	oral use	500 mg
		CIPROXIN	750 mg	film-coated tablets	oral use	750 mg
		CIPROXIN	250 mg/5 ml	oral suspension	oral use	50 mg/ml
		CIPROXIN	500 mg/5 ml	oral suspension	oral use	100 mg/ ml

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
		CIPROXIN XR	500 mg	modified release tablets	oral use	500 mg
		CIPROXIN XR	1000 mg	modified release tablets	oral use	1000 mg
Hungary	Bayer Hungária Kft. H-1123 Budapest Alkotás u. 50. Hungary	Ciprobay	250 mg.	film-coated tablets	oral use	250 mg
		Ciprobay	500 mg	film-coated tablets	oral use	500 mg
		Ciprobay	100 mg/50 ml	solution for infusion	intravenous use	2 mg/ml
		Ciprobay	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciprobay	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
Iceland	Bayer Healthcare AG 51368 Leverkusen, Germany	Ciproxin	250 mg	film-coated tablets	oral use	250 mg
		Ciproxin	500 mg	film-coated tablets	oral use	500 mg
		Ciproxin	750 mg	film-coated tablets	oral use	750mg
		Ciproxin	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciproxin	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
Ireland	Bayer Limited The Atrium, Blackthorn Road, Dublin 18, Ireland	Ciproxin	100 mg	film-coated tablets	oral use use	100 mg
		Ciproxin	250 mg	film-coated tablets	oral use use	250 mg
		Ciproxin	500 mg	film-coated tablets	oral use use	500 mg
		Ciproxin	750 mg	film-coated tablets	oral use use	750 mg
		Ciproxin	250 mg/5 ml	oral suspension	oral use use	50 mg/ml
		Ciproxin	500 mg/5 ml	oral suspension	oral use use	100 mg/ml
		Ciproxin	100 mg/50 ml	solution for infusion	intravenous use	2 mg/ml
		Ciproxin	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciproxin	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
Italy	Bayer HealthCare AG D-51368 Leverkusen, Germany	CIFLOX	250 mg	film-coated tablets	oral use	250 mg
		CIFLOX	500 mg	film-coated tablets	oral use	500 mg
	Bayer S.p.A.	CIPROXIN	250 mg	film-coated tablets	oral use	250 mg

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
	Viale Certosa 130 I-20156 Milan Italy	CIPROXIN	500 mg	film-coated tablets	oral use	500 mg
		CIPROXIN	750 mg	film-coated tablets	oral use	750 mg
		CIPROXIN	500 mg	modified release tablets	oral use	500 mg
		CIPROXIN	1000 mg	modified release tablets	oral use	1000 mg
		CIPROXIN	250 mg	oral suspension	oral use	50 mg/ml
		CIPROXIN	500 mg	oral suspension	oral use	100 mg/ml
		CIPROXIN	100 mg/50 ml	solution for infusion	intravenous use	2 mg/ml
		CIPROXIN	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		CIPROXIN	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
Latvia	Not authorised					
Lithuania	Not authorised					
Luxembourg	BAYER SA-NV Avenue Louise 143 Louizalaan 143 B - 1050 Bruxelles-Brussel Belgium	Ciproxine	100 mg/50 ml	solution for infusion	intravenous use	2 mg/ml
		Ciproxine	100 mg	film-coated tablets	oral use	100 mg
		Ciproxine	250 mg	film-coated tablets	oral use	250 mg
		Ciproxine	500 mg	film-coated tablets	oral use	500 mg
		Ciproxine	750 mg	film-coated tablets	oral use	750 mg
		Ciproxine	5 g/100 ml	oral suspension	oral use	250 mg/5 ml
		Ciproxine	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciproxine	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
Malta	Bayer Plc Bayer House. Newbury Berkshire RG14 1JA United Kingdom Trading as: Bayer plc, Bayer Schering Pharma	Ciproxin	250 mg	film-coated tablets	oral use	250 mg
		Ciproxin	500 mg	film-coated tablets	oral use	500 mg
		Ciproxin	100 mg/50 ml	solution for infusion	intravenous use	2 mg/ml
		Ciproxin	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciproxin	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
Netherlands	Bayer BV	Ciproxin	100 mg	film-coated tablets	oral use	100 mg

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
		Ciproxin	250 mg	film-coated tablets	oral use	250 mg
		Ciproxin	500 mg	film-coated tablets	oral use	500 mg
		Ciproxin	750 mg	film-coated tablets	oral use	750 mg
		Ciproxin	5 g/100 ml	oral suspension	oral use	50mg/ml
		Ciproxin	10 g/100 ml	oral suspension	oral use	100mg/ml
		Ciproxin	100 mg/50 ml	solution for infusion	intravenous use	2 mg/ml
		Ciproxin	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciproxin	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
Norway	Bayer HealthCare AG D-513 68 Leverkusen Germany	Ciproxin	250 mg	film-coated tablets	oral use	250 mg
		Ciproxin	500 mg	film-coated tablets	oral use	500 mg
		Ciproxin	750 mg	film-coated tablets	oral use	750 mg
		Ciproxin	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciproxin	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
Poland	Bayer HealthCare AG D-51368 Leverkusen Germany	Ciprobay Uro	100 mg	film-coated tablet	oral use	100 mg
		Ciprobay	250 mg	film-coated tablet	oral use	250 mg
		Ciprobay	500 mg	film-coated tablet	oral use	500 mg
		Ciprobay	100 mg/50 ml	solution for infusion	intravenous use	2 mg/ml
		Ciprobay	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciprobay	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
Portugal	Bayer Portugal, S.A. Rua Quinta do Pinheiro 5 2794-003 Carnaxide Portugal	Ciproxina	250 mg	film-coated tablets	oral use	250 mg
		Ciproxina	500 mg	film-coated tablets	oral use	500 mg
		Ciproxina	750 mg	film-coated tablets	oral use	750 mg
		Ciproxina OD	500 mg	modified release tablets	oral use	500 mg
		Ciproxina OD	1000 mg	modified release tablets	oral use	1000 mg
		Ciproxina	10 g/100 ml	oral suspension	oral use	100 mg/ ml
		Ciproxina	5 g/100 ml	oral suspension	oral use	50 mg/ml
		Ciproxina	200 mg/100 ml	solution for infusion	intravenous use	2 mg / ml

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
		Ciproxina	400 mg/200 ml	solution for infusion	intravenous use	2 mg / ml
Romania	Bayer HealthCare AG D-51368 Leverkusen Germany	Ciprobay	500 mg	film-coated tablets	oral use	500 mg
		Ciprobay	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciprobay	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
		Ciprobay XR	500 mg	modified release tablets	oral use	500 mg
		Ciprobay XR	1000 mg	modified release tablets	oral use	1000 mg
		Ciproxin	5 g/100 ml	oral suspension	oral use	50 mg/ml
		Ciproxin	10 g/100 ml	oral suspension	oral use	100 mg/ml
Slovak Republic	Bayer HealthCare AG D-51368 Leverkusen Germany	Ciprobay	250 mg	film-coated tablet	oral use	250 mg
		Ciprobay	500 mg	film-coated tablet	oral use	500 mg
		Ciprobay	750 mg	film-coated tablet	oral use	750 mg
		Ciprobay	100 mg/50 ml	solution for infusion	intravenous use	2 mg/ml
		Ciprobay	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciprobay	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
Slovenia	Bayer Pharma, d.o.o., Bravničarjeva 13 SI-1000 Ljubljana Slovenia	Ciprobay	250 mg	film-coated tablet	oral use	250 mg
		Ciprobay	500 mg	film-coated tablet	oral use	500 mg
		Ciprobay	750 mg	film-coated tablet	oral use	750 mg
		Ciprobay	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciprobay	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
Spain	Química Farmacéutica Bayer, S.L. Av. Baix Llobregat, 3-5	BAYCIP	250 mg	film-coated tablets	oral use	250 mg
		BAYCIP	500 mg	film-coated tablets	oral use	500 mg
		BAYCIP	750 mg	film-coated tablets	oral use	750 mg

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
	08970 Sant Joan Despí Barcelona Spain	BAYCIP	250 mg	oral suspension (in single dose sachets)	oral use	250 mg
		BAYCIP	500 mg	oral suspension (in single dose sachets)	oral use	500 mg
		BAYCIP	10 g/100 ml	oral suspension	oral use	100 mg/ml
Sweden	Bayer HealthCare AG D-51368 Leverkusen Germany	Ciproxin	250 mg	film-coated tablet	oral use	250 mg
		Ciproxin	500 mg	film-coated tablet	oral use	500 mg
		Ciproxin	750 mg	film-coated tablet	oral use	750 mg
		Ciproxin	5 g/100 ml	oral suspension	oral use	50 mg/ml
		Ciproxin	10 g/100 ml	oral suspension	oral use	100 mg/ml
		Ciproxin	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciproxin	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml
United Kingdom	Bayer Plc Bayer House. Newbury Berkshire RG14 1JA United Kingdom Trading as: Bayer plc, Bayer Schering Pharma	Ciproxin	100 mg	film-coated tablet	oral use	100 mg
		Ciproxin	250 mg	film-coated tablet	oral use	250 mg
		Ciproxin	500 mg	film-coated tablet	oral use	500 mg
		Ciproxin	750 mg	film-coated tablet	oral use	750 mg
		Ciproxin	250 mg/5 ml	oral suspension	oral use	50 mg/ml
		Ciproxin	500 mg/5 ml	oral suspension	oral use	100 mg/ml
		Ciproxin	100 mg/50 ml	solution for infusion	intravenous use	2 mg/ml
		Ciproxin	200 mg/100 ml	solution for infusion	intravenous use	2 mg/ml
		Ciproxin	400 mg/200 ml	solution for infusion	intravenous use	2 mg/ml

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF CIPROFLOXACIN BAYER AND ASSOCIATED NAMES (SEE ANNEX I)

Ciprofloxacin is a broad spectrum antibacterial agent that belongs to the fluoroquinolone family. It has a long history of known safety and efficacy in adults, children and adolescents. Ciprofloxacin is approved for the treatment of uncomplicated and complicated infections caused by ciprofloxacin-susceptible bacteria and thus a broad variety of infections in adults. Indications approved for children and adolescents in most European countries include acute pulmonary exacerbations of patients with cystic fibrosis caused by *Pseudomonas aeruginosa*, complicated urinary tract infections, pyelonephritis, and post-exposure prophylaxis of inhalational anthrax. To date, ciprofloxacin has been the fluoroquinolone that has been used most extensively in adolescents.

The following oral and intravenous formulations are currently approved and marketed in different EU countries:
- Immediate release film-coated tablets: 100 mg, 250 mg, 500 mg, 750 mg
- Granules and solvent for oral suspension: 250 mg/5 ml, 500 mg/5 ml
- Solution for infusion (glass bottles and flexibags): 100 mg/50 ml, 200 mg/100 ml and 400 mg/200 ml
- Modified release film-coated tablets: 500 mg, 1000 mg.
- Sachets: 250mg, 500mg

The following sections of the Product Information were addressed during this harmonisation procedure.

SPC Section 4.1 Therapeutic Indications
Overall, the CHMP harmonised this section, providing particular attention to the available information on resistance to ciprofloxacin for each indication.

Withdrawn Indications
Overall, the CHMP considered that the therapeutic indication "acute sinusitis" could not be accepted, as the most commonly involved pathogen in this infection, *Streptococcus pneumoniae*, is only intermediately susceptible to ciprofloxacin and its efficacy in this indication is poorly substantiated by the submitted data.

The CHMP considered that the therapeutic indication "septicaemia due to Gram negative bacteria" could not be accepted as the Applicant/MAH did not provide reassurance on the fact that ciprofloxacin could be viewed as an adequate option in this severe situation with regards its level of activity and the available therapeutic alternatives.

The CHMP was of the opinion that the therapeutic indication "selective digestive decontamination in immuno-suppressed patients" could not be accepted, as there is an absence of specific data submitted by the Applicant/MAH to support such therapeutic use and there is no consensus in the scientific community on the use ciprofloxacin in such indication.

Single-dose treatment of uncomplicated UTI:
The CHMP had concerns with regards to the therapeutic indication "single dose treatment of uncomplicated UTI". The single dose treatment of uncomplicated UTI should not be approved unless scientifically justified (comparative benefit/risk assessment with the 3 day treatment regimen is provided). The Applicant/MAH did not provide any data or scientific discussion to support the single dose oral ciprofloxacin treatment of uncomplicated cystitis. In particular, the Applicant/MAH did not discuss its benefit-risk ratio in comparison to the other longer treatment duration (3 day treatment).

However, after extensive discussions, the CHMP considered that ciprofloxacin still remains a useful therapeutic option in uncomplicated cystitis. Even if a 3-day treatment has some advantages in efficacy, the 500 mg single-dose therapy still has a place in the strategy provided its use is adequately

guided by the clinical status of the patients and diagnostic tools. Therefore, both strategies in the treatment of uncomplicated cystitis were considered noteworthy in the oral ciprofloxacin MAA. After a long discussion, an agreement was achieved to using precautionary statements for downgrading the recommendation of the single dose regimen as compared to the 3-day regimen and by restricting this possible option to uncomplicated cystitis in pre-menopausal women.

Treatment of Shigellosis:
The CHMP raised concerns on the potential uncontrolled use of ciprofloxacin in the empirical treatment of shigellosis or traveller's diarrhoea and questioned its effectiveness, especially in the mild form, pointing out the high risk of resistance induction. After evaluating the data presented by the Applicant/MAH, the CHMP considered that the therapeutic indication related to the empiric ciprofloxacin treatment of Shigellosis or the traveller's diarrhoea was acceptable with the wording *"infections of the gastro-intestinal tract (e.g. travellers' diarrhoea)"* and restricted its use in "severe" cases in section 4.2, with the following schedule regimens:

-Diarrhoea caused by bacterial pathogens including Shigella spp. other than Shigella dysenteria type 1and empirical treatment of traveller's diarrhoea (per os : 2 x 500 mg/d - 1 day, i.v : 2 x 400 mg/d – 1 day)
-Diarrhoea caused by Shigella dysenteriae type 1 (per os : 2 x 500 mg/d - 5 days, i.v : 2x400 mg/d- 5 days)

Additionally, the following statement was recommended in section 4.4: *Caution is advised when treating traveller's diarrhea especially if the travel concerns countries a high rate of ciprofloxacin resistant Shigella is observed*.

Infection of bone and joint infections due to Gram-positive bacteria:
The CHMP asked the applicant/MAH to discuss the extent to which ciprofloxacin could be viewed as an acceptable option for treating bone and joints infections due to Gram-positive bacteria (in particular Staphyloccocus species). The response document included a review of clinical data (published data, medical research reports) and microbiological data.

From the data presented, ciprofloxacin prescriptions in "bone and joint infections" were supported by several clinical studies and an extensive use in clinical practice. Nevertheless the CHMP noted that consideration should be given to the precautions of use in ciprofloxacin treatment of such infections. *Staphylococci* or *Pseudomonas aeruginosa* are the main bacteria involved in these infections and ciprofloxacin bacterial activity had to be taken into account regarding these targeted species. Consequently ciprofloxacin should be used only after microbiological documentation and empirical treatment was not recommended. Ciprofloxacin should be used in combination with other antimicrobial agents, such as rifampicin in infections due to Staphylococci, and beta-lactams or aminoglycosides in infections due to *Pseudomonas aeruginosa*.

Therefore, the CHMP considered that the data provided was sufficient to include the therapeutic indication *"Infections of the bones and joints"* in Ciprofloxacin Marketing Authorisations, and noted that the SPC should give a clear message on the need for co-administration with appropriate antibacterial agent(s).

Treatment or prophylaxis in patients with severe neutropenia:
The CHMP asked the applicant/MAH to discuss the extent to which ciprofloxacin could be viewed as an acceptable option in the treatment or prophylaxis in patients with severe neutropenia. The applicant/MAH provided documentation to support the use of ciprofloxacin as a valuable therapeutic option both prophylaxis and treatment of febrile neutropenic patients. In summary, for prophylaxis in neutropenic patients, a 500 mg bid ciprofloxacin dosage regimen was recommended. For treatment of febrile neutropenic patients, when an intravenous antibiotic administration is necessary, ciprofloxacin should be administered at a 400 mg bid or tid regimen. When a switch down to oral therapy is possible, a 750 mg bid ciprofloxacin regimen is recommended. In patients with low-risk neutropenic

fever, a 750 mg bid ciprofloxacin regimen can also be used. In most cases, ciprofloxacin should be administered in combination with another appropriate (beta-lactam) antibiotic.

With regards to the treatment of febrile patients with neutropenia, the CHMP considered that, despite the lack of robustness of the available data (limited number of patients included in these studies), the use of ciprofloxacin remained well admitted in the scientific community and had become part of the clinical practice. The combination with other antibiotics, or its use as monotherapy could be considered adequate. The resort to combination therapy, however, should be envisaged according to specific factors (including severe neutropenia). The adequacy of the therapeutic strategy between monotherapy and combination therapy should be re-considered as soon as microbiological results become available and local guidelines should allow to adequately adapt the ciprofloxacin use. Therefore, the following statement was recommended in Section 4.2 of the SPC: "ciprofloxacin should be co-administered with appropriate antibacterial agents in accordance to official guidance".

With regards to the prophylaxis in neutropenic patients, the studies submitted by the Applicant/MAH showed comparable results between treatment groups. Additionally, the use of ciprofloxacin in prophylaxis of neutropenia was further supported by a recent trial with other fluoroquinolones (levofloxacin). Such a prescription should be handled by specialists in the field and local and national guidelines are available to promote the good use of ciprofloxacin in such situation.

In summary, the CHMP considers that both indications (curative treatment and prophylaxis) were acceptable. In line with the data submitted, the benefit/risk in prophylaxis was regarded as favourable in patients with neutrophil count less than 1000/mm3. The CHMP therefore recommended the following wording to distinguish, by specific indications, the prophylactic and curative uses of ciprofloxacin in neutropenic patients with the following wording:
-treatment of infections in neutropenic patients,
-prophylaxis of infections in neutropenic patients.

Treatment of infections caused by Bacillus Anthracis
The CHMP asked the Applicant/MAH to provide an updated review of the non clinical data (including animal data) and on the clinical experience gained up to now in the use of ciprofloxacin in inhalation anthrax. The Applicant/MAH provided reports summarizing the results of a literature search from 2001 to 2006, including animal model and clinical articles. Referring to the lack of clinical data to support the use of ciprofloxacin in anthrax, the applicant/MAH proposed a statement in section 5.1.

However, the CHMP considered that the particular context of anthrax (i.e.bioterrorism) required deviation from the usual requirement of clinical data and the benefit assessment. Indeed, ciprofloxacin is part of the drugs recommended in the European strategy targeted on treatments and prophylaxis when biological agents are used as weapons of bioterrorism. With regards to inhalation, intestinal and cutaneous anthrax, EMEA proposed guidelines in 2002 including the recommended use of ciprofloxacin in a first line treatment.

In summary, the CHMP was of the opinion that anthrax should remain part of the indications to avoid any confusion for prescribers and to be consistent with EU and international guidelines including a recommendation on ciprofloxacin as a first line treatment. The proposed wording of the therapeutic indications was as follows: "Inhalation anthrax (post exposure prophylaxis and curative treatment)" for oral and IV pharmaceutical presentations. A statement in section 5.1 referring to this indication was also recommended as follows:

Studies have been conducted in experimental animal infections due to inhalations of Bacillus anthracis spores; these studies reveal that antibiotics starting early after exposition, avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose.
The recommended use in human subjects is based primarily on in vitro susceptibility and on animal experimental data together with limited human data. Two -month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent

anthrax infection in humans. The treating physician is referred to national and /or international consensus documents regarding treatment of anthrax

Prophylaxis of invasive infections of adults due to Neisseria meningitides
Ciprofloxacin is used in clinical practice in prophylaxis of invasive infections of adults due to Neisseria meningitidis when rifampicin is contra-indicated or after microbiologically documentation when Neisseria meningitidis is resistant to rifampicin, in line with some therapeutic guidelines. Such a use is supported by publications and clinical experience. The CHMP asked the applicant/MAH to provide a substantiated discussion on the use of ciprofloxacin in prophylaxis of invasive infections of adults, to harmonize the therapeutic management of patients.

After a careful review of the data submitted the CHMP considered that the therapeutic indication of ciprofloxacin in prophylaxis of invasive infections due to Neisseria meningitidis in adults was well substantiated by publications and corresponded to the current practice. Ciprofloxacin should be used only when the resort to rifampcicin is not possible. As it is not compulsory to specify the recommended antibiotic strategy in the wording of the therapeutic indication in the Marketing Authorisation, the CHMP recommended that the proposed 4.1 SPC wording "prophylaxis of invasive infections due to Neisseria meningitidis" remain, and accepted the adult posology: PO: 1 x 500 mg/d (single dose). However, this indication was not considered acceptable for the IV ciprofloxacin formulation.

Restriction of the indication "Infections of the lower respiratory tract"
The CHMP noted that ciprofloxacin was not suited for therapy of pneumococci and its efficacy against chlamydia was worse compared to other fluoroquinolones such as levofloxacin or moxifloxacin. Therefore, the CHMP requested that an appropriate restriction of the indication be made. The indication was reworded to state ciprofloxacin's utility in Gram negative bacterial infections of the lower respiratory track causing exacerbations of chronic obstructive pulmonary disease, bronchopulmonary infections in cystic fibrosis or in bronchiectasis and pneumonia. Therefore the following wording was recommended:
"Lower respiratory tract infections due to Gram negative bacteria:
- exacerbations of chronic obstructive pulmonary disease
- broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
- pneumonia"

Other Indications
The CHMP agreed to simplify the wording for other indications and adapt them to the current epidemiological concerns. Consequently, the following wording was recommended in section 4.1, and subsequently section 4.2 was amended accordingly:
- acute exacerbations of chronic sinusistis especially if these are caused by Gram-negative bacteria
- gonococcal urethritis and cervicitis
- epididymo-orchitis including cases due to Neisseria gonorrhoeae
- pelvic inflammatory disease including cases due to Neisseria gonorrhoeae
- malignant external otitis

Use of Ciprofloxacin in Children and Adolescents
The CHMP raised concerns on the following wording in Section 4.1 of the SPC : *"Other severe infections in accordance with Official guidance, after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify a ciprofloxacin use."* It was deemed to describe clinical situations in which the use of ciprofloxacin may be considered in spite of a missing indication, in children and adolescents. The CHMP initially proposed to put this information in section 4.4 under the subheading "Children and adolescents". However, after careful deliberations, an agreement was reach to include a statement in section 4.1 to cover the possible resort of ciprofloxacin in severe infections with a cross reference in section 4.4 that details such situations. Therefore, the following wording was proposed for section 4.1: *Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to be necessary. Treatment should be initiated only by physicians who are*

experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents (see sections 4.4 and 5.1).

SPC Section 4.2 Posology and method of administration

Posology for severe respiratory tract infections, severe bone and joint infections
In severe respiratory tract infections as well as in severe bone and joint infections, higher doses than that currently recommended (such as 750 mg x 3/day or 1000 mg x 2/day) for oral route are currently used in clinical practice given the known decreased susceptibility of the main pathogens involved (including Pseudomonas aeruginosa, Acinetobacter, Staphylococcus aureus) and the severity of the disease (as well as the difficulties in reaching optimal concentration at the bone level). Therefore, the CHMP asked the applicant/MAH to discuss (PK/PD rational) and make a proposal in this field. However, the recommendation of the administration of 750 mg tid and 1g bid by oral route in severe infections (respiratory tract infections, bone and joint infections) was not supported by the data submitted and the CHMP considered that none of the proposed posologies could be included in the Marketing Authorisation.

Long-term safety profile of ciprofloxacin to treat bone and joint infections
Since a treatment duration of up to 3 months may be required in clinical practice to treat bone and joints infections, the CHMP requested that the applicant/MAH provide long term safety data to substantiate the safety profile of the drug in such a prolonged use. The applicant/MAH submitted 11 studies (8 published clinical studies and 3 medical study reports) in which treatment duration for ciprofloxacin ranged from 2 and 476 days. No new safety concerns arose from these data. Most reported adverse events were not unexpected, mainly gastro-intestinal disorders or cutaneous disorders. In addition, taking into account the large use of ciprofloxacin in post-marketing, no safety signal was identified with long-term use of ciprofloxacin in PSURs. Therefore, the CHMP agreed that the safety data did not show any evidence that the safety profile of ciprofloxacin is affected by a longer treatment duration up to 3 months.

Posology in the treatment of upper respiratory tract infections
The CHMP asked the applicant/MAH to further substantiate the efficacy/risk of the lower dosage proposed (500 mg BID) in the treatment of upper respiratory tract infection, especially with regard to malignant external otitis. From the data submitted the CHMP considered that 500 mg bid could be used in the oral treatment of upper respiratory tract infections such as acute exacerbations of chronic sinusitis and chronic suppurative otitis media. The recommended dosage can be higher (750 mg bid) depending on the severity and the microorganism. However, 500 mg bid PO was considered inadequate for the treatment of malignant external otitis, and a dose of 750 mg bid PO was recommended for oral administration.

Long-term safety profile of ciprofloxacin to treat upper-respiratory tract infections
The CHMP requested that applicant/MAH provide the rationale for a 3-month treatment duration of upper respiratory tract infections and substantiate the long-term safety of the drug in such a prolonged use. In general, treatment of upper respiratory tract infections requires short courses of antibiotic therapy. In studies supporting the use of oral ciprofloxacin in acute exacerbation of chronic sinusitis and exacerbation of chronic otitis media, the treatment duration was 10 days and efficacy results have shown that this duration was sufficient.

However, for infections such as malignant external otitis (MEO), the scenario is different. It is an often intractable bacterial infection of the ear, mastoid and skull base caused by Pseudomonas aeruginosa. The infection typically occurs in elderly diabetic patient and is thought to arise at the osseous-cartilaginous junction. Typically, the infection spreads to the basis of the skull and mastoid, resulting in cranial neuropathies, and rarely, brain abscess, sphenoidal sinusitis. The mean treatment duration of ciprofloxacin for MEO as reported in the meta-analysis on 13 publications, published by Gehanno (1993) was 3 months (6 months in 3 studies, 2 months in one study). Additional studies

submitted also considered that the optimal duration of antibiotic administration may be as long as 8 to 12 weeks in view of the recalcitrant nature of the infection.

Therefore, the CHMP and the Applicant/MAH were in agreement that a duration up to 3 months with ciprofloxacin was justified for the treatment of malignant external otitis. The CHMP also considers that the safety data do not show any evidence that the safety profile of ciprofloxacin is affected by a longer treatment duration up to 3 months.

Posology for the treatment of infections due to Vibrio cholerae
The CHMP asked the Applicant/MAH to justify the suggested dosage regimen for the treatment of infections caused by Vibrio cholerae (oral and iv formulations). In its original document the applicant/MAH proposed an oral posology of 500 mg QD and an IV posology of 200 mgx2. However, these proposals were not in line with the bioequivalence data. The Applicant/MAH subsequently proposed to follow the same proposal for other diarrhoea indications, taking into account data supporting oral 500 mg bid daily dose and considering bioavailability purposes, the corresponding IV dosage should be 400 mg bid. The CHMP agreed with this last Applicant/MAH proposal which is in line with the bioequivalence data.

Posology for the treatment of uncomplicated cystitis
The CHMP asked the applicant/MAH to provide reassurance that a 100 mg BID dose for 3 days (currently validated in some EU countries) is adequate for treating uncomplicated cystitis in young women with regards to the epidemiological figure pertaining to the bacteria potentially involved and with regards to the treatment response as compared to the proposed higher dose of 250 mg- 500 mg BID.

After careful evaluation, the CHMP agreed with the Applicant/MAH to delete the dose regimen "100 mg bid for 3 days" allocated to the treatment of uncomplicated cystitis. Considering risk of failures and taking into account epidemiological concerns due to this sub-optimal schedule, this posology could not be recommended

Dose adjustments for patients with impaired renal function
The CHMP reviewed the Applicant/MAH's initial proposal for dose adjustment in case of renal impairment and considered it incomplete and poorly substantiated. Therefore, the CHMP requested a revised proposal with specific documentation in support.

Subsequently, the CHMP reached an agreement with the Applicant/MAH concerning the new proposals for dose adjustments in case of renal impairment.

Other Sections of the SPC
The following sections of the SPC were also subject to extensive harmonisation during this referral procedure, namely sections 4.4 Special warnings and precautions, 4.5 Interactions, 4.6 Pregnancy and lactation, 4.8 Undesirable effects, 4.9 Overdose, 5.1 Pharmacodynamic properties, and 5.2 Pharmacokinetic properties.

Package Leaflet and Labelling
The changes to the SPC have been taken into account in the amendments to the Package Leaflet and Labelling.

Modified Release Tablets Formulation
Regarding the modified release tablet SPC, no proposal for a harmonised SPC was provided. The Applicant/MAH proposed to take the Ciprofloxacin Modified Release Tablets out of this Referral procedure to significantly simplify the exercise of harmonisation. Given the fact that several EU member states have rejected the MR tablet Marketing Authorisations due to a negative benefit/risk, and taking into consideration that only 5 countries approved this pharmaceutical formulation, no consensual recommendation on the SPC wording could be provided at a European level on the basis of this present Article 30 Referral procedure.

Therefore, the CHMP and the Applicant/MAH were in agreement with the proposal to adapt the national SPCs of Ciprofloxacin MR tablets in those European Member States where the product is approved, to the outcome of the referral procedure for the other Ciprofloxacin Bayer formulations by submitting adequate national variations. Importantly, the MR tablet formulation would not gain any new indications. Only those indications already present in the current MR tablets SPC would be subsequently harmonised to the individually agreed wording of each corresponding indication as per the outcome of the Article 30 Referral.

GROUNDS FOR AMENDMENT OF THE SUMMARY(IES) OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics, labelling and package leaflet.

- the Summaries of Products Characteristic, labelling and package leaflet proposed by the Marketing Authorisation Holders have been assessed based on the documentation submitted and the scientific discussion within the Committee,

- the CHMP concluded that the Marketing Authorisation could be harmonised on the following indications for oral and intravenous formulations in adults:

- Lower respiratory tract infections due to Gram-negative bacteria:
  - Exacerbations of chronic obstructive pulmonary disease
  - Broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
  - Pneumonia
- Chronic suppurative otitis media
- Acute exacerbations of chronic sinusitis, especially if these are caused by Gram-negative bacteria
- Urinary tract infections
- Gonococcal urethritis and cervicitis (only for oral formulations)
- Epididymo-orchitis, including cases due to *Neisseria gonorrhoeae*
- Pelvic inflammatory disease including cases due to *Neisseria gonorrhoeae*
- Infections of the gastro-intestinal tract (e.g. travellers' diarrhoea)
- Intra-abdominal infections
- Infections of the skin and soft tissue caused by Gram-negative bacteria
- Malignant external otitis
- Infections of the bone and joints
- Treatment of infections in neutropenic patients
- Prophylaxis of infections in neutropenic patients
- Prophylaxis of invasive infections due to *Neisseria meningitides* (only for oral formulations)
- Inhalation anthrax (post-exposure prophylaxis and curative intent)

- the CHMP concluded that the Marketing Authorisation could be harmonised on the following indications for oral and intravenous formulations in children and adolescents:

- Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*.
- Complicated urinary tract infections and pyelonephritis
- Inhalation anthrax (post-exposure prophylaxis and curative intent)

the CHMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Ciprofloxacin Bayer and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 100 mg film-coated tablets
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ciprofloxacin Bayer 100 mg film-coated tablets are indicated for the treatment of the following infections (see sections 4.4 and 5.1). Special attention should be paid to available information on resistance to ciprofloxacin before commencing therapy.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Adults

- Lower respiratory tract infections due to Gram-negative bacteria
  - exacerbations of chronic obstructive pulmonary disease
  - broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
  - pneumonia
- Chronic suppurative otitis media
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
- Urinary tract infections
- Gonococcal uretritis and cervicitis
- Epididymo-orchitis including cases due to *Neisseria gonorrhoeae*
- Pelvic inflammatory disease including cases due to *Neisseria gonorrhoeae*

In the above genital tract infections when thought or known to be due to *Neisseria gonorrhoeae* it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility based on laboratory testing.

- Infections of the gastro-intestinal tract (e.g. travellers' diarrhoea)
- Intra-abdominal infections
- Infections of the skin and soft tissue caused by Gram-negative bacteria

- Malignant external otitis
- Infections of the bones and joints
- Treatment of infections in neutropenic patients
- Prophylaxis of infections in neutropenic patients
- Prophylaxis of invasive infections due to *Neisseria meningitidis*
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Children and adolescents

- Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*
- Complicated urinary tract infections and pyelonephritis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to be necessary.

Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents (see sections 4.4 and 5.1).

4.2 Posology and method of administration

The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to ciprofloxacin of the causative organism(s), the renal function of the patient and, in children and adolescents the body weight.
The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course.
Treatment of infections due to certain bacteria (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* or *Staphylococci)* may require higher ciprofloxacin doses and co-administration with other appropriate antibacterial agents.

Treatment of some infections (e.g. pelvic inflammatory disease, intra-abdominal infections, infections in neutropenic patients and infections of bones and joints) may require co-administration with other appropriate antibacterial agents depending on the pathogens involved.

Adults

Indications		**Daily dose in mg**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Infections of the lower respiratory tract		500 mg twice daily to 750 mg twice daily	7 to 14 days
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	500 mg twice daily to 750 mg twice daily	7 to 14 days
	Chronic suppurative otitis media	500 mg twice daily to 750 mg twice daily	7 to 14 days
	Malignant external otitis	750 mg twice daily	28 days up to 3 months

Indications		**Daily dose in mg**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Urinary tract infections	Uncomplicated cystitis	250 mg twice daily to 500 mg twice daily	3 days
		In pre-menopausal women, 500 mg single dose may be used	
	Complicated cystitis, Uncomplicated pyelonephritis	500 mg twice daily	7 days
	Complicated pyelonephritis	500 mg twice daily to 750 mg twice daily	at least 10 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Prostatitis	500 mg twice daily to 750 mg twice daily	2 to 4 weeks (acute) to 4 to 6 weeks (chronic)
Genital tract infections	Gonococcal uretritis and cervicitis	500 mg as a single dose	1 day (single dose)
	Epididymo-orchitis and pelvic inflammatory diseases	500 mg twice daily to 750 mg twice daily	at least 14 days
Infections of the gastro-intestinal tract and intra-abdominal infections	Diarrhoea caused by bacterial pathogens including *Shigella* spp. other than *Shigella dysenteriae* type 1 and empirical treatment of severe travellers' diarrhoea	500 mg twice daily	1 day
	Diarrhoea caused by *Shigella dysenteriae* type 1	500 mg twice daily	5 days
	Diarrhoea caused by *Vibrio cholerae*	500 mg twice daily	3 days
	Typhoid fever	500 mg twice daily	7 days
	Intra-abdominal infections due to Gram-negative bacteria	500 mg twice daily to 750 mg twice daily	5 to 14 days
Infections of the skin and soft tissue		500 mg twice daily to 750 mg twice daily	7 to 14 days
Bone and joint infections		500 mg twice daily to 750 mg twice daily	max. of 3 months
Treatment of infections or prophylaxis of infections in neutropenic patients Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance.		500 mg twice daily to 750 mg twice daily	Therapy should be continued over the entire period of neutropenia
Prophylaxis of invasive infections due to *Neisseria meningitidis*		500 mg as a single dose	1 day (single dose)

Indications	Daily dose in mg	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure.	500 mg twice daily	60 days from the confirmation of *Bacillus anthracis* exposure

Children and adolescents

Indications	Daily dose in mg	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Cystic fibrosis	20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	10 to 14 days
Complicated urinary tract infections and pyelonephritis	10 mg/kg body weight twice daily to 20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	10 to 21 days
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure.	10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 500 mg per dose.	60 days from the confirmation of *Bacillus anthracis* exposure
Other severe infections	20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	According to the type of infections

Geriatric patients

Geriatric patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.

Renal and hepatic impairment

Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance [mL/min/1.73 m²]	Serum Creatinine [µmol/L]	Oral Dose [mg]
> 60	< 124	See Usual Dosage.
30-60	124 to 168	250-500 mg every 12 h
< 30	> 169	250-500 mg every 24 h
Patients on haemodialysis	> 169	250-500 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	250-500 mg every 24 h

In patients with impaired liver function no dose adjustment is required.

Dosing in children with impaired renal and/or hepatic function has not been studied.

Method of administration

Tablets are to be swallowed unchewed with fluid. They can be taken independent of mealtimes. If taken on an empty stomach, the active substance is absorbed more rapidly. Ciprofloxacin tablets should not be taken with dairy products (e.g. milk, yoghurt) or mineral-fortified fruit-juice (e.g. calcium-fortified orange juice) (see section 4.5).

In severe cases or if the patient is unable to take tablets (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

4.3 Contraindications

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients (see section 6.1).

- Concomitant administration of ciprofloxacin and tizanidine (see section 4.5).

4.4 Special warnings and precautions for use

Severe infections and mixed infections with Gram-positive and anaerobic pathogens
Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections ciprofloxacin must be co-administered with other appropriate antibacterial agents.

Streptococcal Infections (including Streptococcus pneumoniae)
Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Genital tract infections
Epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*. Ciprofloxacin should be co-administered with another appropriate antibacterial agent unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Intra-abdominal infections
There are limited data on the efficacy of ciprofloxacin in the treatment of post-surgical intra-abdominal infections.

Travellers' diarrhoea
The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited.

Infections of the bones and joints
Ciprofloxacin should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation.

Inhalational anthrax
Use in humans is based on *in-vitro* susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of anthrax.

Children and adolescents
The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. Safety data from a randomised double-blind study on ciprofloxacin use in children (ciprofloxacin: n=335, mean age = 6.3 years; comparators: n=349, mean age = 6.2 years; age range = 1 to 17 years) revealed an incidence of suspected drug-related arthropathy (discerned from joint-related clinical signs and symptoms) by Day +42 of 7.2% and 4.6%. Respectively, an incidence of drug-related arthropathy by 1-year follow-up was 9.0% and 5.7%. The increase of suspected drug-related arthropathy cases over time was not statistically significant between groups. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue.

Broncho-pulmonary infections in cystic fibrosis
Clinical trials have included children and adolescents aged 5-17 years. More limited experience is available in treating children between 1 and 5 years of age.

Complicated urinary tract infections and pyelonephritis
Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.
Clinical trials have included children and adolescents aged 1-17 years.

Other specific severe infections
Other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify a ciprofloxacin use.
The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with these infections.

Hypersensitivity
Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose (see section 4.8) and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.

Musculoskeletal System
Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.

Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, as soon as the first 48 hours of treatment. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids (see section 4.8).
At any sign of tendinitis (e.g. painful swelling, inflammation), ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected limb at rest.
Ciprofloxacin should be used with caution in patients with myasthenia gravis (see section 4.8).

Photosensitivity
Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking ciprofloxacin should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment (see section 4.8).

Central Nervous System
Quinolones are known to trigger seizures or lower the seizure threshold. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued (see section 4.8). Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to self-endangering behaviour. In these cases, ciprofloxacin should be discontinued.
Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving ciprofloxacin. Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see section 4.8).

Cardiac disorders
Since ciprofloxacin is associated with cases of QT prolongation (see section 4.8), caution should be exercised when treating patients at risk for torsades de pointes arrhythmia.

Gastrointestinal System
The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment (see section 4.8). In such cases, ciprofloxacin should immediately be discontinued, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.

Renal and urinary system
Crystalluria related to the use of ciprofloxacin has been reported (see section 4.8). Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

Hepatobiliary system
Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see section 4.8). In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued.

Glucose-6-phosphate dehydrogenase deficiency
Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.

Resistance
During or following a course of treatment with ciprofloxacin bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas* species.

Cytochrome P450
Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, ropinirole, tizanidine). Co-administration of ciprofloxacin and tizanidine is contra-indicated. Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5).

Methotrexate
The concomitant use of ciprofloxacin with methotrexate is not recommended (see section 4.5).

Interaction with tests
The *in-vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients currently taking ciprofloxacin.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other products on ciprofloxacin:

Chelation Complex Formation

The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing drugs and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of ciprofloxacin. Consequently, ciprofloxacin should be administered either 1-2 hours before or at least 4 hours after these preparations. The restriction does not apply to antacids belonging to the class of H2 receptor blockers.

Food and Dairy Products

Dietary calcium as part of a meal does not significantly affect absorption. However, the concurrent administration of dairy products or mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice) with ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced.

Probenecid

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.

Effects of ciprofloxacin on other medicinal products:

Tizanidine

Tizanidine must not be administered together with ciprofloxacin (see section 4.3). In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

Theophylline

Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary (see section 4.4).

Other xanthine derivatives

On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivatives were reported.

Phenytoin

Simultaneous administration of ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin such that monitoring of drug levels is recommended.

Oral anticoagulants

Simultaneous administration of ciprofloxacin with warfarin may augment its anti-coagulant effects. There have been many reports of increases in oral anticoagulant activity in patients receiving antibacterial agents, including fluoroquinolones. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the fluoroquinolone to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anticoagulant agent.

Ropinirole

It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, results in an increase of C_{max} and AUC of ropinirole by 60% and 84%, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin (see section 4.4).

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy
The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism / foetus (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

Lactation
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are nausea and diarrhoea.

ADRs derived from clinical studies and post-marketing surveillance with Ciprofloxacin Bayer (oral, intravenous, and sequential therapy) sorted by categories of frequency are listed below. The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin.

System Organ Class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1 000 to < 1/100	**Rare** ≥ 1/10 000 to < 1/1 000	**Very Rare** < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Infections and Infestations		Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4)		
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (life-threatening) (see section 4.4) Serum sickness-like reaction	
Metabolism and Nutrition Disorders		Anorexia	Hyperglycaemia		
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression Hallucinations	Psychotic reactions (see section 4.4)	

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	Frequency not known (cannot be estimated from available data)
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (see section 4.4) Vertigo	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension	Peripheral neuropathy (see section 4.4)
Eye Disorders			Visual disturbances	Visual colour distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss / Hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia, QT prolongation, torsades de pointes *
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Cholestatic icterus Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)	

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	Frequency not known (cannot be estimated from available data)
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions (see section 4.4)	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	
Musculoskeletal, Connective Tissue and Bone Disorders		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) (see section 4.4) Exacerbation of symptoms of myasthenia gravis (see section 4.4)	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria (see section 4.4) Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions		Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Prothrombin level abnormal Increased amylase		

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see section 4.4).

Paediatric patients

The incidence of arthropathy, mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see section 4.4).

4.9 Overdose

An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.
Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has been reported.

Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated. Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02

Mechanism of action:

As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

PK/PD relationship:

Efficacy mainly depends on the relation between the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

Mechanism of resistance:

In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.
Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All *in-vitro* mechanisms of resistance are commonly observed in clinical isolates.
Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to ciprofloxacin.
Plasmid-mediated resistance encoded by qnr-genes has been reported.

Spectrum of antibacterial activity:

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

Microorganisms	Susceptible	Resistant
Enterobacteria	S ≤ 0.5 mg/L	R > 1 mg/L
Pseudomonas	S ≤ 0.5 mg/L	R > 1 mg/L
Acinetobacter	S ≤ 1 mg/L	R > 1 mg/L
Staphylococcus spp.[1]	S ≤ 1 mg/L	R > 1 mg/L

Haemophilus influenzae and Moraxella catarrhalis	S ≤ 0.5 mg/L	R > 0.5 mg/L
Neisseria gonorrhoeae	S ≤ 0.03 mg/L	R > 0.06 mg/L
Neisseria meningitidis	S ≤ 0.03 mg/L	R > 0.06 mg/L
Non-species-related breakpoints*****	S ≤ 0.5 mg/L	R > 1 mg/L

1 *Staphylococcus* spp. - breakpoints for ciprofloxacin relate to high dose therapy.

* Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Groupings of relevant species according to ciprofloxacin susceptibility (for *Streptococcus* species see section 4.4)

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms *Bacillus anthracis* (1)
Aerobic Gram-negative micro-organisms *Aeromonas* spp. *Brucella* spp. *Citrobacter koseri* *Francisella tularensis* *Haemophilus ducreyi* *Haemophilus influenzae** *Legionella* spp. *Moraxella catarrhalis** *Neisseria meningitidis* *Pasteurella* spp. *Salmonella* spp.* *Shigella* spp.* *Vibrio* spp. *Yersinia pestis*
Anaerobic micro-organisms *Mobiluncus*
Other micro-organisms *Chlamydia trachomatis* ($) *Chlamydia pneumoniae* ($) *Mycoplasma hominis* ($) *Mycoplasma pneumoniae* ($)
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* ($) *Staphylococcus* spp.* (2)
Aerobic Gram-negative micro-organisms *Acinetobacter baumannii*$^{+}$ *Burkholderia cepacia*$^{+}$* *Campylobacter* spp.$^{+}$* *Citrobacter freundii** *Enterobacter aerogenes* *Enterobacter cloacae** *Escherichia coli** *Klebsiella oxytoca*

*Klebsiella pneumoniae**
*Morganella morganii**
*Neisseria gonorrhoeae**
*Proteus mirabilis**
*Proteus vulgaris**
Providencia spp.
*Pseudomonas aeruginosa**
Pseudomonas fluorescens
*Serratia marcescens**
Anaerobic micro-organisms
Peptostreptococcus spp.
Propionibacterium acnes
INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms
Actinomyces
Enteroccus faecium
Listeria monocytogenes
Aerobic Gram-negative micro-organisms
Stenotrophomonas maltophilia

Anaerobic micro-organisms Excepted as listed above
Other micro-organisms *Mycoplasma genitalium* *Ureaplasma urealitycum*

* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications

+ Resistance rate ≥ 50% in one or more EU countries

($): Natural intermediate susceptibility in the absence of acquired mechanism of resistance

(1): Studies have been conducted in experimental animal infections due to inhalations of *Bacillus anthracis* spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on *in-vitro* susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and/or international consensus documents regarding treatment of anthrax.

(2): Methicillin-resistant *S. aureus* very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin tablets, ciprofloxacin is absorbed rapidly and extensively, mainly from the small intestine, reaching maximum serum concentrations 1-2 hours later.
Single doses of 100-750 mg produced dose-dependent maximum serum concentrations (C_{max}) between 0.56 and 3.7 mg/L. Serum concentrations increase proportionately with doses up to 1000 mg.
The absolute bioavailability is approximately 70-80%.
A 500 mg oral dose given every 12 hours has been shown to produce an area under the serum concentration-time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours.

Distribution

Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Metabolism

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). The metabolites display *in-vitro* antimicrobial activity but to a lower degree than the parent compound.
Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally. The serum elimination half-life in subjects with normal renal function is approximately 4-7 hours.

Excretion of ciprofloxacin (% of dose)		
	Oral Administration	
	Urine	Faeces
Ciprofloxacin	44.7	25.0
Metabolites (M_1-M_4)	11.3	7.5

Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half lives of ciprofloxacin of up to 12 h.

Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Paediatric patients

The pharmacokinetic data in paediatric patients are limited.

In a study in children C_{max} and AUC were not age-dependent (above one year of age). No notable increase in C_{max} and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C_{max} was 6.1 mg/L (range 4.6-8.3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.7-11.8 mg/L) for children between 1 and 5 years of age. The AUC values were 17.4 mg*h/L (range 11.8-32.0 mg*h/L) and 16.5 mg*h/L (range 11.0-23.8 mg*h/L) in the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4-5 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction.
Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin *in-vitro* and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability:
As reported for other gyrase inhibitors, ciprofloxacin causes damage to the large weight-bearing joints in immature animals. The extent of the cartilage damage varies according to age, species and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs, ciprofloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally.]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally.]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally.]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 250 mg film-coated tablets
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ciprofloxacin Bayer 250 mg film-coated tablets are indicated for the treatment of the following infections (see sections 4.4 and 5.1). Special attention should be paid to available information on resistance to ciprofloxacin before commencing therapy.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Adults

- Lower respiratory tract infections due to Gram-negative bacteria
  - exacerbations of chronic obstructive pulmonary disease
  - broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
  - pneumonia
- Chronic suppurative otitis media
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
- Urinary tract infections
- Gonococcal uretritis and cervicitis
- Epididymo-orchitis including cases due to *Neisseria gonorrhoeae*
- Pelvic inflammatory disease including cases due to *Neisseria gonorrhoeae*

In the above genital tract infections when thought or known to be due to *Neisseria gonorrhoeae* it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility based on laboratory testing.

- Infections of the gastro-intestinal tract (e.g. travellers' diarrhoea)
- Intra-abdominal infections
- Infections of the skin and soft tissue caused by Gram-negative bacteria

- Malignant external otitis
- Infections of the bones and joints
- Treatment of infections in neutropenic patients
- Prophylaxis of infections in neutropenic patients
- Prophylaxis of invasive infections due to *Neisseria meningitidis*
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Children and adolescents

- Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*
- Complicated urinary tract infections and pyelonephritis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to be necessary.

Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents (see sections 4.4 and 5.1).

4.2 Posology and method of administration

The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to ciprofloxacin of the causative organism(s), the renal function of the patient and, in children and adolescents the body weight.
The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course.
Treatment of infections due to certain bacteria (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* or *Staphylococci)* may require higher ciprofloxacin doses and co-administration with other appropriate antibacterial agents.

Treatment of some infections (e.g. pelvic inflammatory disease, intra-abdominal infections, infections in neutropenic patients and infections of bones and joints) may require co-administration with other appropriate antibacterial agents depending on the pathogens involved.

Adults

Indications		**Daily dose in mg**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Infections of the lower respiratory tract		500 mg twice daily to 750 mg twice daily	7 to 14 days
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	500 mg twice daily to 750 mg twice daily	7 to 14 days
	Chronic suppurative otitis media	500 mg twice daily to 750 mg twice daily	7 to 14 days
	Malignant external otitis	750 mg twice daily	28 days up to 3 months

Indications		**Daily dose in mg**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Urinary tract infections	Uncomplicated cystitis	250 mg twice daily to 500 mg twice daily	3 days
		In pre-menopausal women, 500 mg single dose may be used	
	Complicated cystitis, Uncomplicated pyelonephritis	500 mg twice daily	7 days
	Complicated pyelonephritis	500 mg twice daily to 750 mg twice daily	at least 10 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Prostatitis	500 mg twice daily to 750 mg twice daily	2 to 4 weeks (acute) to 4 to 6 weeks (chronic)
Genital tract infections	Gonococcal uretritis and cervicitis	500 mg as a single dose	1 day (single dose)
	Epididymo-orchitis and pelvic inflammatory diseases	500 mg twice daily to 750 mg twice daily	at least 14 days
Infections of the gastro-intestinal tract and intra-abdominal infections	Diarrhoea caused by bacterial pathogens including *Shigella* spp. other than *Shigella dysenteriae* type 1 and empirical treatment of severe travellers' diarrhoea	500 mg twice daily	1 day
	Diarrhoea caused by *Shigella dysenteriae* type 1	500 mg twice daily	5 days
	Diarrhoea caused by *Vibrio cholerae*	500 mg twice daily	3 days
	Typhoid fever	500 mg twice daily	7 days
	Intra-abdominal infections due to Gram-negative bacteria	500 mg twice daily to 750 mg twice daily	5 to 14 days
Infections of the skin and soft tissue		500 mg twice daily to 750 mg twice daily	7 to 14 days
Bone and joint infections		500 mg twice daily to 750 mg twice daily	max. of 3 months
Treatment of infections or prophylaxis of infections in neutropenic patients Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance.		500 mg twice daily to 750 mg twice daily	Therapy should be continued over the entire period of neutropenia
Prophylaxis of invasive infections due to *Neisseria meningitidis*		500 mg as a single dose	1 day (single dose)

Indications	Daily dose in mg	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure.	500 mg twice daily	60 days from the confirmation of *Bacillus anthracis* exposure

Children and adolescents

Indications	Daily dose in mg	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Cystic fibrosis	20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	10 to 14 days
Complicated urinary tract infections and pyelonephritis	10 mg/kg body weight twice daily to 20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	10 to 21 days
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure.	10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 500 mg per dose.	60 days from the confirmation of *Bacillus anthracis* exposure
Other severe infections	20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	According to the type of infections

Geriatric patients

Geriatric patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.

Renal and hepatic impairment

Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance [mL/min/1.73 m²]	Serum Creatinine [µmol/L]	Oral Dose [mg]
> 60	< 124	See Usual Dosage.
30-60	124 to 168	250-500 mg every 12 h
< 30	> 169	250-500 mg every 24 h
Patients on haemodialysis	> 169	250-500 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	250-500 mg every 24 h

In patients with impaired liver function no dose adjustment is required.

Dosing in children with impaired renal and/or hepatic function has not been studied.

Method of administration

Tablets are to be swallowed unchewed with fluid. They can be taken independent of mealtimes. If taken on an empty stomach, the active substance is absorbed more rapidly. Ciprofloxacin tablets should not be taken with dairy products (e.g. milk, yoghurt) or mineral-fortified fruit-juice (e.g. calcium-fortified orange juice) (see section 4.5).

In severe cases or if the patient is unable to take tablets (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

4.3 Contraindications

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients (see section 6.1).

- Concomitant administration of ciprofloxacin and tizanidine (see section 4.5).

4.4 Special warnings and precautions for use

Severe infections and mixed infections with Gram-positive and anaerobic pathogens
Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections ciprofloxacin must be co-administered with other appropriate antibacterial agents.

Streptococcal Infections (including Streptococcus pneumoniae)
Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Genital tract infections
Epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*. Ciprofloxacin should be co-administered with another appropriate antibacterial agent unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Intra-abdominal infections
There are limited data on the efficacy of ciprofloxacin in the treatment of post-surgical intra-abdominal infections.

Travellers' diarrhoea
The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited.

Infections of the bones and joints
Ciprofloxacin should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation.

Inhalational anthrax
Use in humans is based on *in-vitro* susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of anthrax.

Children and adolescents
The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. Safety data from a randomised double-blind study on ciprofloxacin use in children (ciprofloxacin: n=335, mean age = 6.3 years; comparators: n=349, mean age = 6.2 years; age range = 1 to 17 years) revealed an incidence of suspected drug-related arthropathy (discerned from joint-related clinical signs and symptoms) by Day +42 of 7.2% and 4.6%. Respectively, an incidence of drug-related arthropathy by 1-year follow-up was 9.0% and 5.7%. The increase of suspected drug-related arthropathy cases over time was not statistically significant between groups. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue.

Broncho-pulmonary infections in cystic fibrosis
Clinical trials have included children and adolescents aged 5-17 years. More limited experience is available in treating children between 1 and 5 years of age.

Complicated urinary tract infections and pyelonephritis
Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.
Clinical trials have included children and adolescents aged 1-17 years.

Other specific severe infections
Other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify a ciprofloxacin use.
The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with these infections.

Hypersensitivity
Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose (see section 4.8) and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.

Musculoskeletal System
Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.

Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, as soon as the first 48 hours of treatment. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids (see section 4.8).
At any sign of tendinitis (e.g. painful swelling, inflammation), ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected limb at rest.
Ciprofloxacin should be used with caution in patients with myasthenia gravis (see section 4.8).

Photosensitivity
Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking ciprofloxacin should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment (see section 4.8).

Central Nervous System
Quinolones are known to trigger seizures or lower the seizure threshold. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued (see section 4.8). Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to self-endangering behaviour. In these cases, ciprofloxacin should be discontinued.
Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving ciprofloxacin. Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see section 4.8).

Cardiac disorders
Since ciprofloxacin is associated with cases of QT prolongation (see section 4.8), caution should be exercised when treating patients at risk for torsades de pointes arrhythmia.

Gastrointestinal System
The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment (see section 4.8). In such cases, ciprofloxacin should immediately be discontinued, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.

Renal and urinary system
Crystalluria related to the use of ciprofloxacin has been reported (see section 4.8). Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

Hepatobiliary system
Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see section 4.8). In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued.

Glucose-6-phosphate dehydrogenase deficiency
Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.

Resistance
During or following a course of treatment with ciprofloxacin bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas* species.

Cytochrome P450
Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, ropinirole, tizanidine). Co-administration of ciprofloxacin and tizanidine is contra-indicated. Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5).

Methotrexate
The concomitant use of ciprofloxacin with methotrexate is not recommended (see section 4.5).

Interaction with tests
The *in-vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients currently taking ciprofloxacin.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other products on ciprofloxacin:

Chelation Complex Formation

The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing drugs and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of ciprofloxacin. Consequently, ciprofloxacin should be administered either 1-2 hours before or at least 4 hours after these preparations. The restriction does not apply to antacids belonging to the class of H2 receptor blockers.

Food and Dairy Products

Dietary calcium as part of a meal does not significantly affect absorption. However, the concurrent administration of dairy products or mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice) with ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced.

Probenecid

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.

Effects of ciprofloxacin on other medicinal products:

Tizanidine

Tizanidine must not be administered together with ciprofloxacin (see section 4.3). In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

Theophylline

Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary (see section 4.4).

Other xanthine derivatives

On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivatives were reported.

Phenytoin

Simultaneous administration of ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin such that monitoring of drug levels is recommended.

Oral anticoagulants

Simultaneous administration of ciprofloxacin with warfarin may augment its anti-coagulant effects. There have been many reports of increases in oral anticoagulant activity in patients receiving antibacterial agents, including fluoroquinolones. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the fluoroquinolone to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anticoagulant agent.

Ropinirole

It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, results in an increase of C_{max} and AUC of ropinirole by 60% and 84%, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin (see section 4.4).

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy
The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism / foetus (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

Lactation
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are nausea and diarrhoea.

ADRs derived from clinical studies and post-marketing surveillance with Ciprofloxacin Bayer (oral, intravenous, and sequential therapy) sorted by categories of frequency are listed below. The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin.

System Organ Class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1 000 to < 1/100	**Rare** ≥ 1/10 000 to < 1/1 000	**Very Rare** < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Infections and Infestations		Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4)		
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (life-threatening) (see section 4.4) Serum sickness-like reaction	
Metabolism and Nutrition Disorders		Anorexia	Hyperglycaemia		
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression Hallucinations	Psychotic reactions (see section 4.4)	

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	Frequency not known (cannot be estimated from available data)
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (see section 4.4) Vertigo	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension	Peripheral neuropathy (see section 4.4)
Eye Disorders			Visual disturbances	Visual colour distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss / Hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia, QT prolongation, torsades de pointes *
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Cholestatic icterus Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)	

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	Frequency not known (cannot be estimated from available data)
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions (see section 4.4)	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	
Musculoskeletal, Connective Tissue and Bone Disorders		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) (see section 4.4) Exacerbation of symptoms of myasthenia gravis (see section 4.4)	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria (see section 4.4) Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions		Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Prothrombin level abnormal Increased amylase		

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see section 4.4).

Paediatric patients

The incidence of arthropathy, mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see section 4.4).

4.9 Overdose

An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.
Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has been reported.

Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated. Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02

Mechanism of action:

As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

PK/PD relationship:

Efficacy mainly depends on the relation between the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

Mechanism of resistance:

In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.
Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All *in-vitro* mechanisms of resistance are commonly observed in clinical isolates.
Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to ciprofloxacin.
Plasmid-mediated resistance encoded by qnr-genes has been reported.

Spectrum of antibacterial activity:

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

Microorganisms	Susceptible	Resistant
Enterobacteria	S ≤ 0.5 mg/L	R > 1 mg/L
Pseudomonas	S ≤ 0.5 mg/L	R > 1 mg/L
Acinetobacter	S ≤ 1 mg/L	R > 1 mg/L
Staphylococcus spp.[1]	S ≤ 1 mg/L	R > 1 mg/L

Haemophilus influenzae and *Moraxella catarrhalis*	S ≤ 0.5 mg/L	R > 0.5 mg/L
Neisseria gonorrhoeae	S ≤ 0.03 mg/L	R > 0.06 mg/L
Neisseria meningitidis	S ≤ 0.03 mg/L	R > 0.06 mg/L
Non-species-related breakpoints*****	S ≤ 0.5 mg/L	R > 1 mg/L

1 *Staphylococcus* spp. - breakpoints for ciprofloxacin relate to high dose therapy.

* Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Groupings of relevant species according to ciprofloxacin susceptibility (for *Streptococcus* species see section 4.4)

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms *Bacillus anthracis* (1)
Aerobic Gram-negative micro-organisms *Aeromonas* spp. *Brucella* spp. *Citrobacter koseri* *Francisella tularensis* *Haemophilus ducreyi* *Haemophilus influenzae** *Legionella* spp. *Moraxella catarrhalis** *Neisseria meningitidis* *Pasteurella* spp. *Salmonella* spp.*** *Shigella* spp.*** *Vibrio* spp. *Yersinia pestis*
Anaerobic micro-organisms *Mobiluncus*
Other micro-organisms *Chlamydia trachomatis* ($) *Chlamydia pneumoniae* ($) *Mycoplasma hominis* ($) *Mycoplasma pneumoniae* ($)
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* ($) *Staphylococcus* spp. *(2)
Aerobic Gram-negative micro-organisms *Acinetobacter baumannii*$^{+}$ *Burkholderia cepacia*$^{+}$*** *Campylobacter* spp.$^{+}$*** *Citrobacter freundii** *Enterobacter aerogenes* *Enterobacter cloacae** *Escherichia coli** *Klebsiella oxytoca*

*Klebsiella pneumoniae**
*Morganella morganii**
*Neisseria gonorrhoeae**
*Proteus mirabilis**
*Proteus vulgaris**
Providencia spp.
*Pseudomonas aeruginosa**
Pseudomonas fluorescens
*Serratia marcescens**
Anaerobic micro-organisms
Peptostreptococcus spp.
Propionibacterium acnes
INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms
Actinomyces
Enteroccus faecium
Listeria monocytogenes
Aerobic Gram-negative micro-organisms
Stenotrophomonas maltophilia
Anaerobic micro-organisms
Excepted as listed above
Other micro-organisms
Mycoplasma genitalium
Ureaplasma urealitycum
* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications
+ Resistance rate ≥ 50% in one or more EU countries
($): Natural intermediate susceptibility in the absence of acquired mechanism of resistance
(1): Studies have been conducted in experimental animal infections due to inhalations of *Bacillus anthracis* spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on *in-vitro* susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and/or international consensus documents regarding treatment of anthrax.
(2): Methicillin-resistant *S. aureus* very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin tablets, ciprofloxacin is absorbed rapidly and extensively, mainly from the small intestine, reaching maximum serum concentrations 1-2 hours later.
Single doses of 100-750 mg produced dose-dependent maximum serum concentrations (C_{max}) between 0.56 and 3.7 mg/L. Serum concentrations increase proportionately with doses up to 1000 mg.
The absolute bioavailability is approximately 70-80%.
A 500 mg oral dose given every 12 hours has been shown to produce an area under the serum concentration-time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours.

Distribution

Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Metabolism

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). The metabolites display *in-vitro* antimicrobial activity but to a lower degree than the parent compound.
Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally. The serum elimination half-life in subjects with normal renal function is approximately 4-7 hours.

Excretion of ciprofloxacin (% of dose)		
	Oral Administration	
	Urine	**Faeces**
Ciprofloxacin	44.7	25.0
Metabolites (M_1-M_4)	11.3	7.5

Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half lives of ciprofloxacin of up to 12 h.

Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Paediatric patients

The pharmacokinetic data in paediatric patients are limited.

In a study in children C_{max} and AUC were not age-dependent (above one year of age). No notable increase in C_{max} and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C_{max} was 6.1 mg/L (range 4.6-8.3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.7-11.8 mg/L) for children between 1 and 5 years of age. The AUC values were 17.4 mg*h/L (range 11.8-32.0 mg*h/L) and 16.5 mg*h/L (range 11.0-23.8 mg*h/L) in the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4-5 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction.
Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/photocarcinogenicity show a weak photomutagenic or

phototumorigenic effect of ciprofloxacin *in-vitro* and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability:
As reported for other gyrase inhibitors, ciprofloxacin causes damage to the large weight-bearing joints in immature animals. The extent of the cartilage damage varies according to age, species and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs, ciprofloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally.]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally.]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally.]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 500 mg film-coated tablets
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ciprofloxacin Bayer 500 mg film-coated tablets are indicated for the treatment of the following infections (see sections 4.4 and 5.1). Special attention should be paid to available information on resistance to ciprofloxacin before commencing therapy.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Adults

- Lower respiratory tract infections due to Gram-negative bacteria
  - exacerbations of chronic obstructive pulmonary disease
  - broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
  - pneumonia
- Chronic suppurative otitis media
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
- Urinary tract infections
- Gonococcal uretritis and cervicitis
- Epididymo-orchitis including cases due to *Neisseria gonorrhoeae*
- Pelvic inflammatory disease including cases due to *Neisseria gonorrhoeae*

In the above genital tract infections when thought or known to be due to *Neisseria gonorrhoeae* it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility based on laboratory testing.

- Infections of the gastro-intestinal tract (e.g. travellers' diarrhoea)
- Intra-abdominal infections
- Infections of the skin and soft tissue caused by Gram-negative bacteria

- Malignant external otitis
- Infections of the bones and joints
- Treatment of infections in neutropenic patients
- Prophylaxis of infections in neutropenic patients
- Prophylaxis of invasive infections due to *Neisseria meningitidis*
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Children and adolescents

- Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*
- Complicated urinary tract infections and pyelonephritis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to be necessary.

Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents (see sections 4.4 and 5.1).

4.2 Posology and method of administration

The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to ciprofloxacin of the causative organism(s), the renal function of the patient and, in children and adolescents the body weight.
The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course.
Treatment of infections due to certain bacteria (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* or *Staphylococci*) may require higher ciprofloxacin doses and co-administration with other appropriate antibacterial agents.

Treatment of some infections (e.g. pelvic inflammatory disease, intra-abdominal infections, infections in neutropenic patients and infections of bones and joints) may require co-administration with other appropriate antibacterial agents depending on the pathogens involved.

Adults

Indications		**Daily dose in mg**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Infections of the lower respiratory tract		500 mg twice daily to 750 mg twice daily	7 to 14 days
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	500 mg twice daily to 750 mg twice daily	7 to 14 days
	Chronic suppurative otitis media	500 mg twice daily to 750 mg twice daily	7 to 14 days
	Malignant external otitis	750 mg twice daily	28 days up to 3 months

Indications		**Daily dose in mg**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Urinary tract infections	Uncomplicated cystitis	250 mg twice daily to 500 mg twice daily	3 days
		In pre-menopausal women, 500 mg single dose may be used	
	Complicated cystitis, Uncomplicated pyelonephritis	500 mg twice daily	7 days
	Complicated pyelonephritis	500 mg twice daily to 750 mg twice daily	at least 10 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Prostatitis	500 mg twice daily to 750 mg twice daily	2 to 4 weeks (acute) to 4 to 6 weeks (chronic)
Genital tract infections	Gonococcal uretritis and cervicitis	500 mg as a single dose	1 day (single dose)
	Epididymo-orchitis and pelvic inflammatory diseases	500 mg twice daily to 750 mg twice daily	at least 14 days
Infections of the gastro-intestinal tract and intra-abdominal infections	Diarrhoea caused by bacterial pathogens including *Shigella* spp. other than *Shigella dysenteriae* type 1 and empirical treatment of severe travellers' diarrhoea	500 mg twice daily	1 day
	Diarrhoea caused by *Shigella dysenteriae* type 1	500 mg twice daily	5 days
	Diarrhoea caused by *Vibrio cholerae*	500 mg twice daily	3 days
	Typhoid fever	500 mg twice daily	7 days
	Intra-abdominal infections due to Gram-negative bacteria	500 mg twice daily to 750 mg twice daily	5 to 14 days
Infections of the skin and soft tissue		500 mg twice daily to 750 mg twice daily	7 to 14 days
Bone and joint infections		500 mg twice daily to 750 mg twice daily	max. of 3 months
Treatment of infections or prophylaxis of infections in neutropenic patients Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance.		500 mg twice daily to 750 mg twice daily	Therapy should be continued over the entire period of neutropenia
Prophylaxis of invasive infections due to *Neisseria meningitidis*		500 mg as a single dose	1 day (single dose)

Indications	Daily dose in mg	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure.	500 mg twice daily	60 days from the confirmation of *Bacillus anthracis* exposure

Children and adolescents

Indications	Daily dose in mg	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Cystic fibrosis	20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	10 to 14 days
Complicated urinary tract infections and pyelonephritis	10 mg/kg body weight twice daily to 20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	10 to 21 days
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure.	10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 500 mg per dose.	60 days from the confirmation of *Bacillus anthracis* exposure
Other severe infections	20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	According to the type of infections

Geriatric patients

Geriatric patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.

Renal and hepatic impairment

Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance [mL/min/1.73 m²]	Serum Creatinine [µmol/L]	Oral Dose [mg]
> 60	< 124	See Usual Dosage.
30-60	124 to 168	250-500 mg every 12 h
< 30	> 169	250-500 mg every 24 h
Patients on haemodialysis	> 169	250-500 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	250-500 mg every 24 h

In patients with impaired liver function no dose adjustment is required.

Dosing in children with impaired renal and/or hepatic function has not been studied.

Method of administration

Tablets are to be swallowed unchewed with fluid. They can be taken independent of mealtimes. If taken on an empty stomach, the active substance is absorbed more rapidly. Ciprofloxacin tablets should not be taken with dairy products (e.g. milk, yoghurt) or mineral-fortified fruit-juice (e.g. calcium-fortified orange juice) (see section 4.5).

In severe cases or if the patient is unable to take tablets (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

4.3 Contraindications

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients (see section 6.1).
- Concomitant administration of ciprofloxacin and tizanidine (see section 4.5).

4.4 Special warnings and precautions for use

Severe infections and mixed infections with Gram-positive and anaerobic pathogens
Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections ciprofloxacin must be co-administered with other appropriate antibacterial agents.

Streptococcal Infections (including Streptococcus pneumoniae)
Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Genital tract infections
Epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*. Ciprofloxacin should be co-administered with another appropriate antibacterial agent unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Intra-abdominal infections
There are limited data on the efficacy of ciprofloxacin in the treatment of post-surgical intra-abdominal infections.

Travellers' diarrhoea
The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited.

Infections of the bones and joints
Ciprofloxacin should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation.

Inhalational anthrax
Use in humans is based on *in-vitro* susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of anthrax.

Children and adolescents
The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. Safety data from a randomised double-blind study on ciprofloxacin use in children (ciprofloxacin: n=335, mean age = 6.3 years; comparators: n=349, mean age = 6.2 years; age range = 1 to 17 years) revealed an incidence of suspected drug-related arthropathy (discerned from joint-related clinical signs and symptoms) by Day +42 of 7.2% and 4.6%. Respectively, an incidence of drug-related arthropathy by 1-year follow-up was 9.0% and 5.7%. The increase of suspected drug-related arthropathy cases over time was not statistically significant between groups. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue.

Broncho-pulmonary infections in cystic fibrosis
Clinical trials have included children and adolescents aged 5-17 years. More limited experience is available in treating children between 1 and 5 years of age.

Complicated urinary tract infections and pyelonephritis
Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.
Clinical trials have included children and adolescents aged 1-17 years.

Other specific severe infections
Other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify a ciprofloxacin use.
The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with these infections.

Hypersensitivity
Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose (see section 4.8) and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.

Musculoskeletal System
Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.

Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, as soon as the first 48 hours of treatment. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids (see section 4.8).
At any sign of tendinitis (e.g. painful swelling, inflammation), ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected limb at rest.
Ciprofloxacin should be used with caution in patients with myasthenia gravis (see section 4.8).

Photosensitivity
Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking ciprofloxacin should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment (see section 4.8).

Central Nervous System
Quinolones are known to trigger seizures or lower the seizure threshold. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued (see section 4.8). Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to self-endangering behaviour. In these cases, ciprofloxacin should be discontinued.
Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving ciprofloxacin. Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see section 4.8).

Cardiac disorders
Since ciprofloxacin is associated with cases of QT prolongation (see section 4.8), caution should be exercised when treating patients at risk for torsades de pointes arrhythmia.

Gastrointestinal System
The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment (see section 4.8). In such cases, ciprofloxacin should immediately be discontinued, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.

Renal and urinary system
Crystalluria related to the use of ciprofloxacin has been reported (see section 4.8). Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

Hepatobiliary system
Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see section 4.8). In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued.

Glucose-6-phosphate dehydrogenase deficiency
Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.

Resistance
During or following a course of treatment with ciprofloxacin bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas* species.

Cytochrome P450
Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, ropinirole, tizanidine). Co-administration of ciprofloxacin and tizanidine is contra-indicated. Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5).

Methotrexate
The concomitant use of ciprofloxacin with methotrexate is not recommended (see section 4.5).

Interaction with tests
The *in-vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients currently taking ciprofloxacin.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other products on ciprofloxacin:

Chelation Complex Formation

The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing drugs and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of ciprofloxacin. Consequently, ciprofloxacin should be administered either 1-2 hours before or at least 4 hours after these preparations. The restriction does not apply to antacids belonging to the class of H2 receptor blockers.

Food and Dairy Products

Dietary calcium as part of a meal does not significantly affect absorption. However, the concurrent administration of dairy products or mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice) with ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced.

Probenecid

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.

Effects of ciprofloxacin on other medicinal products:

Tizanidine

Tizanidine must not be administered together with ciprofloxacin (see section 4.3). In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

Theophylline

Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary (see section 4.4).

Other xanthine derivatives

On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivatives were reported.

Phenytoin

Simultaneous administration of ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin such that monitoring of drug levels is recommended.

Oral anticoagulants

Simultaneous administration of ciprofloxacin with warfarin may augment its anti-coagulant effects. There have been many reports of increases in oral anticoagulant activity in patients receiving antibacterial agents, including fluoroquinolones. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the fluoroquinolone to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anticoagulant agent.

Ropinirole

It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, results in an increase of C_{max} and AUC of ropinirole by 60% and 84%, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin (see section 4.4).

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy
The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism / foetus (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

Lactation
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are nausea and diarrhoea.

ADRs derived from clinical studies and post-marketing surveillance with Ciprofloxacin Bayer (oral, intravenous, and sequential therapy) sorted by categories of frequency are listed below. The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin.

System Organ Class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1 000 to < 1/100	**Rare** ≥ 1/10 000 to < 1/1 000	**Very Rare** < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Infections and Infestations		Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4)		
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (life-threatening) (see section 4.4) Serum sickness-like reaction	
Metabolism and Nutrition Disorders		Anorexia	Hyperglycaemia		
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression Hallucinations	Psychotic reactions (see section 4.4)	

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	Frequency not known (cannot be estimated from available data)
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (see section 4.4) Vertigo	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension	Peripheral neuropathy (see section 4.4)
Eye Disorders			Visual disturbances	Visual colour distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss / Hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia, QT prolongation, torsades de pointes *
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Cholestatic icterus Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)	

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	Frequency not known (cannot be estimated from available data)
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions (see section 4.4)	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	
Musculoskeletal, Connective Tissue and Bone Disorders		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) (see section 4.4) Exacerbation of symptoms of myasthenia gravis (see section 4.4)	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria (see section 4.4) Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions		Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Prothrombin level abnormal Increased amylase		

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see section 4.4).

Paediatric patients

The incidence of arthropathy, mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see section 4.4).

4.9 Overdose

An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.
Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has been reported.

Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated. Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02

Mechanism of action:

As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

PK/PD relationship:

Efficacy mainly depends on the relation between the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

Mechanism of resistance:

In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.
Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All *in-vitro* mechanisms of resistance are commonly observed in clinical isolates.
Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to ciprofloxacin.
Plasmid-mediated resistance encoded by qnr-genes has been reported.

Spectrum of antibacterial activity:

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

Microorganisms	Susceptible	Resistant
Enterobacteria	S ≤ 0.5 mg/L	R > 1 mg/L
Pseudomonas	S ≤ 0.5 mg/L	R > 1 mg/L
Acinetobacter	S ≤ 1 mg/L	R > 1 mg/L
Staphylococcus spp.[1]	S ≤ 1 mg/L	R > 1 mg/L

Haemophilus influenzae and *Moraxella catarrhalis*	S ≤ 0.5 mg/L	R > 0.5 mg/L
Neisseria gonorrhoeae	S ≤ 0.03 mg/L	R > 0.06 mg/L
Neisseria meningitidis	S ≤ 0.03 mg/L	R > 0.06 mg/L
Non-species-related breakpoints*****	S ≤ 0.5 mg/L	R > 1 mg/L

1 *Staphylococcus* spp. - breakpoints for ciprofloxacin relate to high dose therapy.

* Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Groupings of relevant species according to ciprofloxacin susceptibility (for *Streptococcus* species see section 4.4)

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms *Bacillus anthracis* (1)
Aerobic Gram-negative micro-organisms *Aeromonas* spp. *Brucella* spp. *Citrobacter koseri* *Francisella tularensis* *Haemophilus ducreyi* *Haemophilus influenzae** *Legionella* spp. *Moraxella catarrhalis** *Neisseria meningitidis* *Pasteurella* spp. *Salmonella* spp.* *Shigella* spp.* *Vibrio* spp. *Yersinia pestis*
Anaerobic micro-organisms *Mobiluncus*
Other micro-organisms *Chlamydia trachomatis* ($) *Chlamydia pneumoniae* ($) *Mycoplasma hominis* ($) *Mycoplasma pneumoniae* ($)
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* ($) *Staphylococcus* spp.* (2)
Aerobic Gram-negative micro-organisms *Acinetobacter baumannii*$^{+}$ *Burkholderia cepacia*$^{+}$* *Campylobacter* spp.$^{+}$* *Citrobacter freundii** *Enterobacter aerogenes* *Enterobacter cloacae** *Escherichia coli** *Klebsiella oxytoca* *Klebsiella pneumoniae** *Morganella morganii** *Neisseria gonorrhoeae** *Proteus mirabilis** *Proteus vulgaris** *Providencia* spp. *Pseudomonas aeruginosa** *Pseudomonas fluorescens* *Serratia marcescens**
Anaerobic micro-organisms *Peptostreptococcus* spp. *Propionibacterium acnes*
INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms *Actinomyces* *Enteroccus faecium* *Listeria monocytogenes*

Aerobic Gram-negative micro-organisms *Stenotrophomonas maltophilia*
Anaerobic micro-organisms *Excepted as listed above*
Other micro-organisms *Mycoplasma genitalium* *Ureaplasma urealitycum*
* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications + Resistance rate ≥ 50% in one or more EU countries ($): Natural intermediate susceptibility in the absence of acquired mechanism of resistance (1): Studies have been conducted in experimental animal infections due to inhalations of *Bacillus anthracis* spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on *in-vitro* susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and/or international consensus documents regarding treatment of anthrax. (2): Methicillin-resistant *S. aureus* very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin tablets, ciprofloxacin is absorbed rapidly and extensively, mainly from the small intestine, reaching maximum serum concentrations 1-2 hours later.
Single doses of 100-750 mg produced dose-dependent maximum serum concentrations (C_{max}) between 0.56 and 3.7 mg/L. Serum concentrations increase proportionately with doses up to 1000 mg.
The absolute bioavailability is approximately 70-80%.
A 500 mg oral dose given every 12 hours has been shown to produce an area under the serum concentration-time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours.

Distribution

Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Metabolism

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). The metabolites display *in-vitro* antimicrobial activity but to a lower degree than the parent compound.
Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally. The serum elimination half-life in subjects with normal renal function is approximately 4-7 hours.

Excretion of ciprofloxacin (% of dose)		
	Oral Administration	
	Urine	Faeces
Ciprofloxacin	44.7	25.0
Metabolites (M_1-M_4)	11.3	7.5

Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half lives of ciprofloxacin of up to 12 h.

Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Paediatric patients

The pharmacokinetic data in paediatric patients are limited.

In a study in children C_{max} and AUC were not age-dependent (above one year of age). No notable increase in C_{max} and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C_{max} was 6.1 mg/L (range 4.6-8.3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.7-11.8 mg/L) for children between 1 and 5 years of age. The AUC values were 17.4 mg*h/L (range 11.8-32.0 mg*h/L) and 16.5 mg*h/L (range 11.0-23.8 mg*h/L) in the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4-5 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction.
Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/ photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin *in-vitro* and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability:
As reported for other gyrase inhibitors, ciprofloxacin causes damage to the large weight-bearing joints in immature animals. The extent of the cartilage damage varies according to age, species and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs, ciprofloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally.]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally.]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally.]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 750 mg film-coated tablets
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ciprofloxacin Bayer 750 mg film-coated tablets are indicated for the treatment of the following infections (see sections 4.4 and 5.1). Special attention should be paid to available information on resistance to ciprofloxacin before commencing therapy.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Adults

- Lower respiratory tract infections due to Gram-negative bacteria
  - exacerbations of chronic obstructive pulmonary disease
  - broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
  - pneumonia
- Chronic suppurative otitis media
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
- Urinary tract infections
- Gonococcal uretritis and cervicitis
- Epididymo-orchitis including cases due to *Neisseria gonorrhoeae*
- Pelvic inflammatory disease including cases due to *Neisseria gonorrhoeae*

In the above genital tract infections when thought or known to be due to *Neisseria gonorrhoeae* it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility based on laboratory testing.

- Infections of the gastro-intestinal tract (e.g. travellers' diarrhoea)
- Intra-abdominal infections
- Infections of the skin and soft tissue caused by Gram-negative bacteria

- Malignant external otitis
- Infections of the bones and joints
- Treatment of infections in neutropenic patients
- Prophylaxis of infections in neutropenic patients
- Prophylaxis of invasive infections due to *Neisseria meningitidis*
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Children and adolescents

- Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*
- Complicated urinary tract infections and pyelonephritis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to be necessary.

Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents (see sections 4.4 and 5.1).

4.2 Posology and method of administration

The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to ciprofloxacin of the causative organism(s), the renal function of the patient and, in children and adolescents the body weight.
The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course.
Treatment of infections due to certain bacteria (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* or *Staphylococci) may require* higher ciprofloxacin doses and co-administration with other appropriate antibacterial agents.

Treatment of some infections (e.g. pelvic inflammatory disease, intra-abdominal infections, infections in neutropenic patients and infections of bones and joints) may require co-administration with other appropriate antibacterial agents depending on the pathogens involved.

Adults

Indications		**Daily dose in mg**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Infections of the lower respiratory tract		500 mg twice daily to 750 mg twice daily	7 to 14 days
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	500 mg twice daily to 750 mg twice daily	7 to 14 days
	Chronic suppurative otitis media	500 mg twice daily to 750 mg twice daily	7 to 14 days
	Malignant external otitis	750 mg twice daily	28 days up to 3 months

Indications		**Daily dose in mg**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Urinary tract infections	Uncomplicated cystitis	250 mg twice daily to 500 mg twice daily	3 days
		In pre-menopausal women, 500 mg single dose may be used	
	Complicated cystitis, Uncomplicated pyelonephritis	500 mg twice daily	7 days
	Complicated pyelonephritis	500 mg twice daily to 750 mg twice daily	at least 10 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Prostatitis	500 mg twice daily to 750 mg twice daily	2 to 4 weeks (acute) to 4 to 6 weeks (chronic)
Genital tract infections	Gonococcal uretritis and cervicitis	500 mg as a single dose	1 day (single dose)
	Epididymo-orchitis and pelvic inflammatory diseases	500 mg twice daily to 750 mg twice daily	at least 14 days
Infections of the gastro-intestinal tract and intra-abdominal infections	Diarrhoea caused by bacterial pathogens including *Shigella* spp. other than *Shigella dysenteriae* type 1 and empirical treatment of severe travellers' diarrhoea	500 mg twice daily	1 day
	Diarrhoea caused by *Shigella dysenteriae* type 1	500 mg twice daily	5 days
	Diarrhoea caused by *Vibrio cholerae*	500 mg twice daily	3 days
	Typhoid fever	500 mg twice daily	7 days
	Intra-abdominal infections due to Gram-negative bacteria	500 mg twice daily to 750 mg twice daily	5 to 14 days
Infections of the skin and soft tissue		500 mg twice daily to 750 mg twice daily	7 to 14 days
Bone and joint infections		500 mg twice daily to 750 mg twice daily	max. of 3 months
Treatment of infections or prophylaxis of infections in neutropenic patients Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance.		500 mg twice daily to 750 mg twice daily	Therapy should be continued over the entire period of neutropenia
Prophylaxis of invasive infections due to *Neisseria meningitidis*		500 mg as a single dose	1 day (single dose)

Indications	Daily dose in mg	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure.	500 mg twice daily	60 days from the confirmation of *Bacillus anthracis* exposure

Children and adolescents

Indications	Daily dose in mg	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Cystic fibrosis	20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	10 to 14 days
Complicated urinary tract infections and pyelonephritis	10 mg/kg body weight twice daily to 20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	10 to 21 days
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure.	10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 500 mg per dose.	60 days from the confirmation of *Bacillus anthracis* exposure
Other severe infections	20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	According to the type of infections

Geriatric patients

Geriatric patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.

Renal and hepatic impairment

Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance [mL/min/1.73 m²]	Serum Creatinine [µmol/L]	Oral Dose [mg]
> 60	< 124	See Usual Dosage.
30-60	124 to 168	250-500 mg every 12 h
< 30	> 169	250-500 mg every 24 h
Patients on haemodialysis	> 169	250-500 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	250-500 mg every 24 h

In patients with impaired liver function no dose adjustment is required.

Dosing in children with impaired renal and/or hepatic function has not been studied.

Method of administration

Tablets are to be swallowed unchewed with fluid. They can be taken independent of mealtimes. If taken on an empty stomach, the active substance is absorbed more rapidly. Ciprofloxacin tablets should not be taken with dairy products (e.g. milk, yoghurt) or mineral-fortified fruit-juice (e.g. calcium-fortified orange juice) (see section 4.5).

In severe cases or if the patient is unable to take tablets (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

4.3 Contraindications

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients (see section 6.1).

- Concomitant administration of ciprofloxacin and tizanidine (see section 4.5).

4.4 Special warnings and precautions for use

Severe infections and mixed infections with Gram-positive and anaerobic pathogens
Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections ciprofloxacin must be co-administered with other appropriate antibacterial agents.

Streptococcal Infections (including Streptococcus pneumoniae)
Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Genital tract infections
Epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*. Ciprofloxacin should be co-administered with another appropriate antibacterial agent unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Intra-abdominal infections
There are limited data on the efficacy of ciprofloxacin in the treatment of post-surgical intra-abdominal infections.

Travellers' diarrhoea
The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited.

Infections of the bones and joints
Ciprofloxacin should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation.

Inhalational anthrax
Use in humans is based on *in-vitro* susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of anthrax.

Children and adolescents
The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. Safety data from a randomised double-blind study on ciprofloxacin use in children (ciprofloxacin: n=335, mean age = 6.3 years; comparators: n=349, mean age = 6.2 years; age range = 1 to 17 years) revealed an incidence of suspected drug-related arthropathy (discerned from joint-related clinical signs and symptoms) by Day +42 of 7.2% and 4.6%. Respectively, an incidence of drug-related arthropathy by 1-year follow-up was 9.0% and 5.7%. The increase of suspected drug-related arthropathy cases over time was not statistically significant between groups. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue.

Broncho-pulmonary infections in cystic fibrosis
Clinical trials have included children and adolescents aged 5-17 years. More limited experience is available in treating children between 1 and 5 years of age.

Complicated urinary tract infections and pyelonephritis
Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.
Clinical trials have included children and adolescents aged 1-17 years.

Other specific severe infections
Other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify a ciprofloxacin use.
The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with these infections.

Hypersensitivity
Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose (see section 4.8) and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.

Musculoskeletal System
Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.

Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, as soon as the first 48 hours of treatment. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids (see section 4.8).
At any sign of tendinitis (e.g. painful swelling, inflammation), ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected limb at rest.
Ciprofloxacin should be used with caution in patients with myasthenia gravis (see section 4.8).

Photosensitivity
Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking ciprofloxacin should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment (see section 4.8).

Central Nervous System
Quinolones are known to trigger seizures or lower the seizure threshold. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued (see section 4.8). Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to self-endangering behaviour. In these cases, ciprofloxacin should be discontinued.
Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving ciprofloxacin. Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see section 4.8).

Cardiac disorders
Since ciprofloxacin is associated with cases of QT prolongation (see section 4.8), caution should be exercised when treating patients at risk for torsades de pointes arrhythmia.

Gastrointestinal System
The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment (see section 4.8). In such cases, ciprofloxacin should immediately be discontinued, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.

Renal and urinary system
Crystalluria related to the use of ciprofloxacin has been reported (see section 4.8). Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

Hepatobiliary system
Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see section 4.8). In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued.

Glucose-6-phosphate dehydrogenase deficiency
Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.

Resistance
During or following a course of treatment with ciprofloxacin bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas* species.

Cytochrome P450
Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, ropinirole, tizanidine). Co-administration of ciprofloxacin and tizanidine is contra-indicated. Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5).

Methotrexate
The concomitant use of ciprofloxacin with methotrexate is not recommended (see section 4.5).

Interaction with tests
The *in-vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients currently taking ciprofloxacin.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other products on ciprofloxacin:

Chelation Complex Formation

The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing drugs and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of ciprofloxacin. Consequently, ciprofloxacin should be administered either 1-2 hours before or at least 4 hours after these preparations. The restriction does not apply to antacids belonging to the class of H2 receptor blockers.

Food and Dairy Products

Dietary calcium as part of a meal does not significantly affect absorption. However, the concurrent administration of dairy products or mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice) with ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced.

Probenecid

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.

Effects of ciprofloxacin on other medicinal products:

Tizanidine

Tizanidine must not be administered together with ciprofloxacin (see section 4.3). In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

Theophylline

Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary (see section 4.4).

Other xanthine derivatives

On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivatives were reported.

Phenytoin

Simultaneous administration of ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin such that monitoring of drug levels is recommended.

Oral anticoagulants

.Simultaneous administration of ciprofloxacin with warfarin may augment its anti-coagulant effects. There have been many reports of increases in oral anticoagulant activity in patients receiving antibacterial agents, including fluoroquinolones. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the fluoroquinolone to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anticoagulant agent.

Ropinirole

It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, results in an increase of C_{max} and AUC of ropinirole by 60% and 84%, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin (see section 4.4).

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy
The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism / foetus (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

Lactation
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are nausea and diarrhoea.

ADRs derived from clinical studies and post-marketing surveillance with Ciprofloxacin Bayer (oral, intravenous, and sequential therapy) sorted by categories of frequency are listed below. The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin.

System Organ Class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1 000 to < 1/100	**Rare** ≥ 1/10 000 to < 1/1 000	**Very Rare** < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Infections and Infestations		Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4)		
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (life-threatening) (see section 4.4) Serum sickness-like reaction	
Metabolism and Nutrition Disorders		Anorexia	Hyperglycaemia		
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression Hallucinations	Psychotic reactions (see section 4.4)	

System Organ Class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1 000 to < 1/100	**Rare** ≥ 1/10 000 to < 1/1 000	**Very Rare** < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (see section 4.4) Vertigo	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension	Peripheral neuropathy (see section 4.4)
Eye Disorders			Visual disturbances	Visual colour distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss / Hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia, QT prolongation, torsades de pointes *
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Cholestatic icterus Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)	

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	Frequency not known (cannot be estimated from available data)
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions (see section 4.4)	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	
Musculoskeletal, Connective Tissue and Bone Disorders		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) (see section 4.4) Exacerbation of symptoms of myasthenia gravis (see section 4.4)	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria (see section 4.4) Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions		Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Prothrombin level abnormal Increased amylase		

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see section 4.4).

Paediatric patients

The incidence of arthropathy, mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see section 4.4).

4.9 Overdose

An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.
Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has been reported.

Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated. Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02

Mechanism of action:

As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

PK/PD relationship:

Efficacy mainly depends on the relation between the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

Mechanism of resistance:

In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.
Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All *in-vitro* mechanisms of resistance are commonly observed in clinical isolates.
Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to ciprofloxacin.
Plasmid-mediated resistance encoded by qnr-genes has been reported.

Spectrum of antibacterial activity:

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

Microorganisms	Susceptible	Resistant
Enterobacteria	S ≤ 0.5 mg/L	R > 1 mg/L
Pseudomonas	S ≤ 0.5 mg/L	R > 1 mg/L
Acinetobacter	S ≤ 1 mg/L	R > 1 mg/L
Staphylococcus spp.[1]	S ≤ 1 mg/L	R > 1 mg/L

Haemophilus influenzae and *Moraxella catarrhalis*	S ≤ 0.5 mg/L	R > 0.5 mg/L
Neisseria gonorrhoeae	S ≤ 0.03 mg/L	R > 0.06 mg/L
Neisseria meningitidis	S ≤ 0.03 mg/L	R > 0.06 mg/L
Non-species-related breakpoints*****	S ≤ 0.5 mg/L	R > 1 mg/L

1 *Staphylococcus* spp. - breakpoints for ciprofloxacin relate to high dose therapy.

* Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Groupings of relevant species according to ciprofloxacin susceptibility (for *Streptococcus* species see section 4.4)

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms *Bacillus anthracis* (1)
Aerobic Gram-negative micro-organisms *Aeromonas* spp. *Brucella* spp. *Citrobacter koseri* *Francisella tularensis* *Haemophilus ducreyi* *Haemophilus influenzae** *Legionella* spp. *Moraxella catarrhalis** *Neisseria meningitidis* *Pasteurella* spp. *Salmonella* spp.* *Shigella* spp.* *Vibrio* spp. *Yersinia pestis*
Anaerobic micro-organisms *Mobiluncus*
Other micro-organisms *Chlamydia trachomatis* ($) *Chlamydia pneumoniae* ($) *Mycoplasma hominis* ($) *Mycoplasma pneumoniae* ($)
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* ($) *Staphylococcus* spp. *(2)
Aerobic Gram-negative micro-organisms *Acinetobacter baumannii*$^{+}$ *Burkholderia cepacia*$^{+}$* *Campylobacter* spp.$^{+}$* *Citrobacter freundii** *Enterobacter aerogenes* *Enterobacter cloacae** *Escherichia coli** *Klebsiella oxytoca* *Klebsiella pneumoniae** *Morganella morganii** *Neisseria gonorrhoeae** *Proteus mirabilis** *Proteus vulgaris** *Providencia* spp. *Pseudomonas aeruginosa** *Pseudomonas fluorescens* *Serratia marcescens**
Anaerobic micro-organisms *Peptostreptococcus* spp. *Propionibacterium acnes*
INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms *Actinomyces* *Enteroccus faecium* *Listeria monocytogenes*

Aerobic Gram-negative micro-organisms *Stenotrophomonas maltophilia*
Anaerobic micro-organisms *Excepted as listed above*
Other micro-organisms *Mycoplasma genitalium* *Ureaplasma urealitycum*

* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications

$^{+}$ Resistance rate ≥ 50% in one or more EU countries

($): Natural intermediate susceptibility in the absence of acquired mechanism of resistance

(1): Studies have been conducted in experimental animal infections due to inhalations of *Bacillus anthracis* spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on *in-vitro* susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and/or international consensus documents regarding treatment of anthrax.

(2): Methicillin-resistant *S. aureus* very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin tablets, ciprofloxacin is absorbed rapidly and extensively, mainly from the small intestine, reaching maximum serum concentrations 1-2 hours later.
Single doses of 100-750 mg produced dose-dependent maximum serum concentrations (C_{max}) between 0.56 and 3.7 mg/L. Serum concentrations increase proportionately with doses up to 1000 mg.
The absolute bioavailability is approximately 70-80%.
A 500 mg oral dose given every 12 hours has been shown to produce an area under the serum concentration-time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours.

Distribution

Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Metabolism

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). The metabolites display *in-vitro* antimicrobial activity but to a lower degree than the parent compound.
Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally. The serum elimination half-life in subjects with normal renal function is approximately 4-7 hours.

Excretion of ciprofloxacin (% of dose)		
	Oral Administration	
	Urine	**Faeces**
Ciprofloxacin	44.7	25.0
Metabolites (M_1-M_4)	11.3	7.5

Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half lives of ciprofloxacin of up to 12 h.

Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Paediatric patients

The pharmacokinetic data in paediatric patients are limited.

In a study in children C_{max} and AUC were not age-dependent (above one year of age). No notable increase in C_{max} and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C_{max} was 6.1 mg/L (range 4.6-8.3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.7-11.8 mg/L) for children between 1 and 5 years of age. The AUC values were 17.4 mg*h/L (range 11.8-32.0 mg*h/L) and 16.5 mg*h/L (range 11.0-23.8 mg*h/L) in the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4-5 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction.
Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin *in-vitro* and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability:
As reported for other gyrase inhibitors, ciprofloxacin causes damage to the large weight-bearing joints in immature animals. The extent of the cartilage damage varies according to age, species and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs, ciprofloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally.]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally.]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally.]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 250 mg oral suspension in single-dose sachets
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension (in single-dose sachets)
[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The Ciprofloxacin Bayer 250 mg oral suspension in single-dose sachets are indicated for the treatment of the following infections (see sections 4.4 and 5.1). Special attention should be paid to available information on resistance to ciprofloxacin before commencing therapy.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Adults

- Lower respiratory tract infections due to Gram-negative bacteria
  - exacerbations of chronic obstructive pulmonary disease
  - broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
  - pneumonia
- Chronic suppurative otitis media
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
- Urinary tract infections
- Gonococcal uretritis and cervicitis
- Epididymo-orchitis including cases due to *Neisseria gonorrhoeae*
- Pelvic inflammatory disease including cases due to *Neisseria gonorrhoeae*

In the above genital tract infections when thought or known to be due to *Neisseria gonorrhoeae* it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility based on laboratory testing.

- Infections of the gastro-intestinal tract (e.g. travellers' diarrhoea)
- Intra-abdominal infections
- Infections of the skin and soft tissue caused by Gram-negative bacteria

- Malignant external otitis
- Infections of the bones and joints
- Treatment of infections in neutropenic patients
- Prophylaxis of infections in neutropenic patients
- Prophylaxis of invasive infections due to *Neisseria meningitidis*
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Children and adolescents

- Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*
- Complicated urinary tract infections and pyelonephritis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to be necessary.

Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents (see sections 4.4 and 5.1).

4.2 Posology and method of administration

The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to ciprofloxacin of the causative organism(s), the renal function of the patient and, in children and adolescents the body weight.
The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course.
Treatment of infections due to certain bacteria (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* or *Staphylococci*) may require higher ciprofloxacin doses and co-administration with other appropriate antibacterial agents.

Treatment of some infections (e.g. pelvic inflammatory disease, intra-abdominal infections, infections in neutropenic patients and infections of bones and joints) may require co-administration with other appropriate antibacterial agents depending on the pathogens involved.

Adults

Indications		**Daily dose in mg**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Infections of the lower respiratory tract		500 mg twice daily to 750 mg twice daily	7 to 14 days
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	500 mg twice daily to 750 mg twice daily	7 to 14 days
	Chronic suppurative otitis media	500 mg twice daily to 750 mg twice daily	7 to 14 days
	Malignant external otitis	750 mg twice daily	28 days up to 3 months

Indications		**Daily dose in mg**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Urinary tract infections	Uncomplicated cystitis	250 mg twice daily to 500 mg twice daily	3 days
		In pre-menopausal women, 500 mg single dose may be used	
	Complicated cystitis, Uncomplicated pyelonephritis	500 mg twice daily	7 days
	Complicated pyelonephritis	500 mg twice daily to 750 mg twice daily	at least 10 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Prostatitis	500 mg twice daily to 750 mg twice daily	2-4 weeks (acute) to 4-6 weeks (chronic)
Genital tract infections	Gonococcal uretritis and cervicitis	500 mg as a single dose	1 day (single dose)
	Epididymo-orchitis and pelvic inflammatory diseases	500 mg twice daily to 750 mg twice daily	at least 14 days
Infections of the gastro-intestinal tract and intra-abdominal infections	Diarrhoea caused by bacterial pathogens including *Shigella* spp. other than *Shigella dysenteriae* type 1 and empirical treatment of severe travellers' diarrhoea	500 mg twice daily	1 day
	Diarrhoea caused by *Shigella dysenteriae* type 1	500 mg twice daily	5 days
	Diarrhoea caused by *Vibrio cholerae*	500 mg twice daily	3 days
	Typhoid fever	500 mg twice daily	7 days
	Intra-abdominal infections due to Gram-negative bacteria	500 mg twice daily to 750 mg twice daily	5 to 14 days
Infections of the skin and soft tissue		500 mg twice daily to 750 mg twice daily	7 to 14 days
Bone and joint infections		500 mg twice daily to 750 mg twice daily	max. of 3 months
Treatment of infections or prophylaxis of infections in neutropenic patients Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance.		500 mg twice daily to 750 mg twice daily	Therapy should be continued over the entire period of neutropenia
Prophylaxis of invasive infections due to *Neisseria meningitidis*		500 mg as a single dose	1 day (single dose)
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate.		500 mg twice daily	60 days from the confirmation of *Bacillus anthracis* exposure

Indications	Daily dose in mg	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Drug administration should begin as soon as possible after suspected or confirmed exposure.		

Children and adolescents

Indications	Daily dose in mg	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Cystic fibrosis	20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	10 to 14 days
Complicated urinary tract infections and pyelonephritis	10 mg/kg body weight twice daily to 20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	10 to 21 days
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure.	10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 500 mg per dose.	60 days from the confirmation of *Bacillus anthracis* exposure
Other severe infections	20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	According to the type of infections

Geriatric patients

Geriatric patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.

Renal and hepatic impairment

Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance [mL/min/1.73 m²]	Serum Creatinine [µmol/L]	Oral Dose [mg]
> 60	< 124	See Usual Dosage.
30-60	124 to 168	250-500 mg every 12 h
< 30	> 169	250-500 mg every 24 h
Patients on haemodialysis	> 169	250-500 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	250-500 mg every 24 h

In patients with impaired liver function no dose adjustment is required.

Dosing in children with impaired renal and/or hepatic function has not been studied.

Method of administration

Oral suspension in single-dose sachets can be taken independent of mealtimes.

If taken on an empty stomach, the active substance is absorbed more rapidly. Ciprofloxacin should not be taken with dairy products (e.g. milk, yoghurt) or mineral-fortified fruit juice (e.g. calcium-fortified orange juice) (see section 4.5).

In severe cases or if the patient is unable to take oral suspension (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

4.3 Contraindications

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients (see section 6.1).

- Concomitant administration of ciprofloxacin and tizanidine (see section 4.5).

4.4 Special warnings and precautions for use

Severe infections and mixed infections with Gram-positive and anaerobic pathogens
Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections ciprofloxacin must be co-administered with other appropriate antibacterial agents.

Streptococcal Infections (including Streptococcus pneumoniae)
Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Genital tract infections
Epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*. Ciprofloxacin should be co-administered with another appropriate antibacterial agent unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Intra-abdominal infections
There are limited data on the efficacy of ciprofloxacin in the treatment of post-surgical intra-abdominal infections.

Travellers' diarrhoea

The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited.

Infections of the bones and joints
Ciprofloxacin should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation.

Inhalational anthrax
Use in humans is based on *in-vitro* susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and /or international consensus documents regarding the treatment of anthrax.

Children and adolescents
The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. Safety data from a randomised double-blind study on ciprofloxacin use in children (ciprofloxacin: n=335, mean age = 6.3 years; comparators: n=349, mean age = 6.2 years; age range = 1 to 17 years) revealed an incidence of suspected drug-related arthropathy (discerned from joint-related clinical signs and symptoms) by Day +42 of 7.2% and 4.6%. Respectively, an incidence of drug-related arthropathy by 1-year follow-up was 9.0% and 5.7%. The increase of suspected drug-related arthropathy cases over time was not statistically significant between groups. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue.

Broncho-pulmonary infections in cystic fibrosis
Clinical trials have included children and adolescents aged 5-17 years. More limited experience is available in treating children between 1 and 5 years of age.

Complicated urinary tract infections and pyelonephritis
Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.
Clinical trials have included children and adolescents aged 1-17 years.

Other specific severe infections
Other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify a ciprofloxacin use.
The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with these infections.

Hypersensitivity
Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose (see section 4.8) and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.

Musculoskeletal System
Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.

Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, as soon as the first 48 hours of treatment. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids (see section 4.8).
At any sign of tendinitis (e.g. painful swelling, inflammation), ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected limb at rest.
Ciprofloxacin should be used with caution in patients with myasthenia gravis (see section 4.8).

Photosensitivity
Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking ciprofloxacin should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment (see section 4.8).

Central Nervous System
Quinolones are known to trigger seizures or lower the seizure threshold. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued (see section 4.8). Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to self-endangering behaviour. In these cases, ciprofloxacin should be discontinued.
Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving ciprofloxacin. Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see section 4.8).

Cardiac disorders
Since ciprofloxacin is associated with cases of QT prolongation (see section 4.8), caution should be exercised when treating patients at risk for torsades de pointes arrhythmia.

Gastrointestinal System
The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment (see section 4.8). In such cases, ciprofloxacin should immediately be discontinued, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.

Renal and urinary system
Crystalluria related to the use of ciprofloxacin has been reported (see section 4.8). Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

Hepatobiliary system
Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see section 4.8). In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued.

Glucose-6-phosphate dehydrogenase deficiency
Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.

Resistance
During or following a course of treatment with ciprofloxacin bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas* species.

Cytochrome P450
Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, ropinirole, tizanidine). Co-administration of ciprofloxacin and tizanidine is contra-indicated. Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5).

Methotrexate
The concomitant use of ciprofloxacin with methotrexate is not recommended (see section 4.5).

Interaction with tests
The *in-vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients currently taking ciprofloxacin.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other products on ciprofloxacin:

Chelation Complex Formation

The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing drugs and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of ciprofloxacin. Consequently, ciprofloxacin should be administered either 1-2 hours before or at least 4 hours after these preparations. The restriction does not apply to antacids belonging to the class of H2 receptor blockers.

Food and Dairy Products

Dietary calcium as part of a meal does not significantly affect absorption. However, the concurrent administration of dairy products or mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice) with ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced.

Probenecid

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.

Effects of ciprofloxacin on other medicinal products:

Tizanidine

Tizanidine must not be administered together with ciprofloxacin (see section 4.3). In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

Theophylline

Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary (see section 4.4).

Other xanthine derivatives

On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivatives were reported.

Phenytoin

Simultaneous administration of ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin such that monitoring of drug levels is recommended.

Oral ant-icoagulants

Simultaneous administration of ciprofloxacin with warfarin may augment its anti-coagulant effects. There have been many reports of increases in oral anti-coagulant activity in patients receiving antibacterial agents, including fluoroquinolones. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the fluoroquinolone to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anti-coagulant agent.

Ropinirole

It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, results in an increase of Cmax and AUC of ropinirole by 60% and 84%, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin (see section 4.4).

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy
The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism / foetus (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

Lactation
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are nausea and diarrhoea.

ADRs derived from clinical studies and post-marketing surveillance with Ciprofloxacin Bayer (oral, intravenous, and sequential therapy) sorted by categories of frequency are listed below. The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin.

System Organ Class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1 000 to < 1/100	**Rare** ≥ 1/10 000 to < 1/1 000	**Very Rare** < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Infections and Infestations		Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4)		
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (life-threatening) (see section 4.4) Serum sickness-like reaction	
Metabolism and Nutrition Disorders		Anorexia	Hyperglycaemia		
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression Hallucinations	Psychotic reactions (see section 4.4)	

System Organ Class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1 000 to < 1/100	**Rare** ≥ 1/10 000 to < 1/1 000	**Very Rare** < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (see section 4.4) Vertigo	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension	Peripheral neuropathy (see section 4.4)
Eye Disorders			Visual disturbances	Visual colour distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss / Hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia, QT prolongation, torsades de pointes *
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Cholestatic icterus Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)	
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions (see section 4.4)	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening)	

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	Frequency not known (cannot be estimated from available data)
				Toxic epidermal necrolysis (potentially life-threatening)	
Musculoskeletal, Connective Tissue and Bone Disorders		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) (see section 4.4) Exacerbation of symptoms of myasthenia gravis (see section 4.4)	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria (see section 4.4) Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions		Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Prothrombin level abnormal Increased amylase		

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see section 4.4).

Paediatric patients

The incidence of arthropathy, mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see section 4.4).

4.9 Overdose

An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.
Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has been reported.

Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated. Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02

Mechanism of action:

As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

PK/PD relationship:

Efficacy mainly depends on the relation between the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

Mechanism of resistance:

In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.
Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All *in-vitro* mechanisms of resistance are commonly observed in clinical isolates.
Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa)* and efflux mechanisms may affect susceptibility to ciprofloxacin. Plasmid-mediated resistance encoded by qnr-genes has been reported.

Spectrum of antibacterial activity:

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

Microorganisms	Susceptible	Resistant
Enterobacteria	S ≤ 0.5 mg/L	R > 1 mg/L
Pseudomonas	S ≤ 0.5 mg/L	R > 1 mg/L
Acinetobacter	S ≤ 1 mg/L	R > 1 mg/L
Staphylococcus spp.[1]	S ≤ 1 mg/L	R > 1 mg/L
Haemophilus influenzae and *Moraxella catarrhalis*	S ≤ 0.5 mg/L	R > 0.5 mg/L
Neisseria gonorrhoeae	S ≤ 0.03 mg/L	R > 0.06 mg/L
Neisseria meningitidis	S ≤ 0.03 mg/L	R > 0.06 mg/L
Non-species-related breakpoints *	S ≤ 0.5 mg/L	R > 1 mg/L

1 *Staphylococcus* spp. - breakpoints for ciprofloxacin relate to high dose therapy.

* Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species

where susceptibility testing is not recommended.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Groupings of relevant species according to ciprofloxacin susceptibility (for *Streptococcus* species see section 4.4)

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms *Bacillus anthracis* (1)
Aerobic Gram-negative micro-organisms *Aeromonas* spp. *Brucella* spp. *Citrobacter koseri* *Francisella tularensis* *Haemophilus ducreyi* *Haemophilus influenzae* * *Legionella* spp. *Moraxella catarrhalis* * *Neisseria meningitidis* *Pasteurella* spp. *Salmonella* spp.* *Shigella* spp.* *Vibrio* spp. *Yersinia pestis*
Anaerobic micro-organisms *Mobiluncus*
Other micro-organisms *Chlamydia trachomatis* ($) *Chlamydia pneumoniae* ($) *Mycoplasma hominis* ($) *Mycoplasma pneumoniae* ($)
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms *Enterococcus faecalis*($) *Staphylococcus* spp.*(2)
Aerobic Gram-negative micro-organisms *Acinetobacter baumannii*$^{+}$ *Burkholderia cepacia*$^{+*}$ *Campylobacter* spp.$^{+}$* *Citrobacter freundii** *Enterobacter aerogenes* *Enterobacter cloacae* * *Escherichia coli** *Klebsiella oxytoca* *Klebsiella pneumoniae** *Morganella morganii** *Neisseria gonorrhoeae** *Proteus mirabilis** *Proteus vulgaris** *Providencia* spp. *Pseudomonas aeruginosa** *Pseudomonas fluorescens* *Serratia marcescens**
Anaerobic micro-organisms *Peptostreptococcus* spp. *Propionibacterium acnes*

INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms *Actinomyces* *Enteroccus faecium* *Listeria monocytogenes*
Aerobic Gram-negative micro-organisms *Stenotrophomonas maltophilia*
Anaerobic micro-organisms *Excepted as listed above*
Other micro-organisms *Mycoplasma genitalium* *Ureaplasma urealitycum*
* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications. + Resistance rate ≥ 50% in one or more EU countries ($): Natural intermediate susceptibility in the absence of acquired mechanism of resistance (1): Studies have been conducted in experimental animal infections due to inhalations of *Bacillus anthracis* spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on *in-vitro* susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and /or international consensus documents regarding treatment of anthrax. (2): Methicillin-resistant *S. aureus* very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin tablets, ciprofloxacin is absorbed rapidly and extensively, mainly from the small intestine, reaching maximum serum concentrations 1-2 hours later.
Single doses of 100-750 mg produced dose-dependent maximum serum concentrations (C_{max}) between 0.56 and 3.7 mg/L. Serum concentrations increase proportionately with doses up to 1000 mg.
The absolute bioavailability is approximately 70-80%.
A 500 mg oral dose given every 12 hours has been shown to produce an area under the serum concentration-time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours.
The pharmacokinetics of ciprofloxacin 250 mg and 500 mg oral suspension in single-dose sachets are similar to those of tablets.

Distribution

Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Metabolism

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). The metabolites display *in-vitro* antimicrobial activity but to a lower degree than the parent compound.
Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally. The serum elimination half-life in subjects with normal renal function is approximately 4-7 hours.

Excretion of ciprofloxacin (% of dose)		
	Oral Administration	
	Urine	**Faeces**
Ciprofloxacin	44.7	25.0
Metabolites (M1-M4)	11.3	7.5

Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half lives of ciprofloxacin of up to 12 h.

Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Paediatric patients

The pharmacokinetic data in paediatric patients are limited.

In a study in children C_{max} and AUC were not age-dependent (above one year of age). No notable increase in C_{max} and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C_{max} was 6.1 mg/L (range 4.6-8.3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.7-11.8 mg/L) for children between 1 and 5 years of age. The AUC values were 17.4 mg*h/L (range 11.8-32.0 mg*h/L) and 16.5 mg*h/L (range 11.0-23.8 mg*h/L) in the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4-5 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction.
Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/ photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin *in-vitro* and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability:
As reported for other gyrase inhibitors, ciprofloxacin causes damage to the large weight-bearing joints in immature animals. The extent of the cartilage damage varies according to age, species and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs, ciprofloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal and other handling

Take the prescribed amount of sachets. Shake the sachet applying slight pressure to the walls. Then tear the sachet open as indicated and take the contents directly.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally.]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally.]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally.]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 500 mg oral suspension in single-dose sachets
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension (in single-dose sachets)
[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The Ciprofloxacin Bayer 500 mg oral suspension in single-dose sachets are indicated for the treatment of the following infections (see sections 4.4 and 5.1). Special attention should be paid to available information on resistance to ciprofloxacin before commencing therapy.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Adults

- Lower respiratory tract infections due to Gram-negative bacteria
  - exacerbations of chronic obstructive pulmonary disease
  - broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
  - pneumonia
- Chronic suppurative otitis media
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
- Urinary tract infections
- Gonococcal uretritis and cervicitis
- Epididymo-orchitis including cases due to *Neisseria gonorrhoeae*
- Pelvic inflammatory disease including cases due to *Neisseria gonorrhoeae*

In the above genital tract infections when thought or known to be due to *Neisseria gonorrhoeae* it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility based on laboratory testing.

- Infections of the gastro-intestinal tract (e.g. travellers' diarrhoea)
- Intra-abdominal infections
- Infections of the skin and soft tissue caused by Gram-negative bacteria

- Malignant external otitis
- Infections of the bones and joints
- Treatment of infections in neutropenic patients
- Prophylaxis of infections in neutropenic patients
- Prophylaxis of invasive infections due to *Neisseria meningitidis*
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Children and adolescents

- Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*
- Complicated urinary tract infections and pyelonephritis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to be necessary.

Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents (see sections 4.4 and 5.1).

4.2 Posology and method of administration

The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to ciprofloxacin of the causative organism(s), the renal function of the patient and, in children and adolescents the body weight.
The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course.
Treatment of infections due to certain bacteria (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* or *Staphylococci)* may require higher ciprofloxacin doses and co-administration with other appropriate antibacterial agents.

Treatment of some infections (e.g. pelvic inflammatory disease, intra-abdominal infections, infections in neutropenic patients and infections of bones and joints) may require co-administration with other appropriate antibacterial agents depending on the pathogens involved.

Adults

Indications		**Daily dose in mg**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Infections of the lower respiratory tract		500 mg twice daily to 750 mg twice daily	7 to 14 days
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	500 mg twice daily to 750 mg twice daily	7 to 14 days
	Chronic suppurative otitis media	500 mg twice daily to 750 mg twice daily	7 to 14 days
	Malignant external otitis	750 mg twice daily	28 days up to 3 months

Indications		**Daily dose in mg**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Urinary tract infections	Uncomplicated cystitis	250 mg twice daily to 500 mg twice daily	3 days
		In pre-menopausal women, 500 mg single dose may be used	
	Complicated cystitis, Uncomplicated pyelonephritis	500 mg twice daily	7 days
	Complicated pyelonephritis	500 mg twice daily to 750 mg twice daily	at least 10 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Prostatitis	500 mg twice daily to 750 mg twice daily	2 to 4 weeks (acute) to 4 to6 weeks (chronic)
Genital tract infections	Gonococcal uretritis and cervicitis	500 mg as a single dose	1 day (single dose)
	Epididymo-orchitis and pelvic inflammatory diseases	500 mg twice daily to 750 mg twice daily	at least 14 days
Infections of the gastro-intestinal tract and intra-abdominal infections	Diarrhoea caused by bacterial pathogens including *Shigella* spp. other than *Shigella dysenteriae* type 1 and empirical treatment of severe travellers' diarrhoea	500 mg twice daily	1 day
	Diarrhoea caused by *Shigella dysenteriae* type 1	500 mg twice daily	5 days
	Diarrhoea caused by *Vibrio cholerae*	500 mg twice daily	3 days
	Typhoid fever	500 mg twice daily	7 days
	Intra-abdominal infections due to Gram-negative bacteria	500 mg twice daily to 750 mg twice daily	5 to 14 days
Infections of the skin and soft tissue		500 mg twice daily to 750 mg twice daily	7 to 14 days
Bone and joint infections		500 mg twice daily to 750 mg twice daily	max. of 3 months
Treatment of infections or prophylaxis of infections in neutropenic patients Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance.		500 mg twice daily to 750 mg twice daily	Therapy should be continued over the entire period of neutropenia
Prophylaxis of invasive infections due to *Neisseria meningitidis*		500 mg as a single dose	1 day (single dose)

Indications	Daily dose in mg	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure.	500 mg twice daily	60 days from the confirmation of *Bacillus anthracis* exposure

Children and adolescents

Indications	Daily dose in mg	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Cystic fibrosis	20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	10 to 14 days
Complicated urinary tract infections and pyelonephritis	10 mg/kg body weight twice daily to 20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	10 to 21 days
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure.	10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 500 mg per dose.	60 days from the confirmation of *Bacillus anthracis* exposure
Other severe infections	20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	According to the type of infections

Geriatric patients

Geriatric patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.

Renal and hepatic impairment

Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance [mL/min/ 1.73 m²]	Serum Creatinine [µmol/L]	Oral Dose [mg]
> 60	< 124	See Usual Dosage.
30-60	124 to 168	250-500 mg every 12 h
< 30	> 169	250-500 mg every 24 h
Patients on haemodialysis	> 169	250-500 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	250-500 mg every 24 h

In patients with impaired liver function no dose adjustment is required.

Dosing in children with impaired renal and/or hepatic function has not been studied.

Method of administration

Oral suspension in single-dose sachets can be taken independent of mealtimes.

If taken on an empty stomach, the active substance is absorbed more rapidly. Ciprofloxacin should not be taken with dairy products (e.g. milk, yoghurt) or mineral-fortified fruit juice (e.g. calcium-fortified orange juice) (see section 4.5).

In severe cases or if the patient is unable to take oral suspension (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

4.3 Contraindications

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients (see section 6.1).

- Concomitant administration of ciprofloxacin and tizanidine (see section 4.5).

4.4 Special warnings and precautions for use

Severe infections and mixed infections with Gram-positive and anaerobic pathogens
Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections ciprofloxacin must be co-administered with other appropriate antibacterial agents.

Streptococcal Infections (including Streptococcus pneumoniae)
Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Genital tract infections
Epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*. Ciprofloxacin should be co-administered with another appropriate antibacterial agent unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Intra-abdominal infections
There are limited data on the efficacy of ciprofloxacin in the treatment of post-surgical intra-abdominal infections.

Travellers' diarrhoea
The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited.

Infections of the bones and joints
Ciprofloxacin should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation.

Inhalational anthrax
Use in humans is based on *in-vitro* susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and /or international consensus documents regarding the treatment of anthrax.

Children and adolescents
The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. Safety data from a randomised double-blind study on ciprofloxacin use in children (ciprofloxacin: n=335, mean age = 6.3 years; comparators: n=349, mean age = 6.2 years; age range = 1 to 17 years) revealed an incidence of suspected drug-related arthropathy (discerned from joint-related clinical signs and symptoms) by Day +42 of 7.2% and 4.6%. Respectively, an incidence of drug-related arthropathy by 1-year follow-up was 9.0% and 5.7%. The increase of suspected drug-related arthropathy cases over time was not statistically significant between groups. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue.

Broncho-pulmonary infections in cystic fibrosis
Clinical trials have included children and adolescents aged 5-17 years. More limited experience is available in treating children between 1 and 5 years of age.

Complicated urinary tract infections and pyelonephritis
Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.
Clinical trials have included children and adolescents aged 1-17 years.

Other specific severe infections
Other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify a ciprofloxacin use.
The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with these infections.

Hypersensitivity
Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose (see section 4.8) and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.

Musculoskeletal System
Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.

Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, as soon as the first 48 hours of treatment. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids (see section 4.8).
At any sign of tendinitis (e.g. painful swelling, inflammation), ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected limb at rest.
Ciprofloxacin should be used with caution in patients with myasthenia gravis (see section 4.8).

Photosensitivity
Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking ciprofloxacin should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment (see section 4.8).

Central Nervous System
Quinolones are known to trigger seizures or lower the seizure threshold. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued (see section 4.8). Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to self-endangering behaviour. In these cases, ciprofloxacin should be discontinued.
Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving ciprofloxacin. Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see section 4.8).

Cardiac disorders
Since ciprofloxacin is associated with cases of QT prolongation (see section 4.8), caution should be exercised when treating patients at risk for torsades de pointes arrhythmia.

Gastrointestinal System
The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment (see section 4.8). In such cases, ciprofloxacin should immediately be discontinued, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.

Renal and urinary system
Crystalluria related to the use of ciprofloxacin has been reported (see section 4.8). Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

Hepatobiliary system
Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see section 4.8). In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued.

Glucose-6-phosphate dehydrogenase deficiency
Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.

Resistance
During or following a course of treatment with ciprofloxacin bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas* species.

Cytochrome P450
Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, ropinirole, tizanidine). Co-administration of ciprofloxacin and tizanidine is contra-indicated. Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5).

Methotrexate
The concomitant use of ciprofloxacin with methotrexate is not recommended (see section 4.5).

Interaction with tests
The *in-vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients currently taking ciprofloxacin.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other products on ciprofloxacin:

Chelation Complex Formation

The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing drugs and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of ciprofloxacin. Consequently, ciprofloxacin should be administered either 1-2 hours before or at least 4 hours after these preparations. The restriction does not apply to antacids belonging to the class of H2 receptor blockers.

Food and Dairy Products

Dietary calcium as part of a meal does not significantly affect absorption. However, the concurrent administration of dairy products or mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice) with ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced.

Probenecid

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.

Effects of ciprofloxacin on other medicinal products:

Tizanidine

Tizanidine must not be administered together with ciprofloxacin (see section 4.3). In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

Theophylline

Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary (see section 4.4).

Other xanthine derivatives

On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivatives were reported.

Phenytoin

Simultaneous administration of ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin such that monitoring of drug levels is recommended.

Oral anticoagulants

Simultaneous administration of ciprofloxacin with warfarin may augment its anti-coagulant effects. There have been many reports of increases in oral anticoagulant activity in patients receiving antibacterial agents, including fluoroquinolones. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the fluoroquinolone to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anticoagulant agent.

Ropinirole

It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, results in an increase of C_{max} and AUC of ropinirole by 60% and 84%, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin (see section 4.4).

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy
The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism / foetus (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

Lactation
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are nausea and diarrhoea.

ADRs derived from clinical studies and post-marketing surveillance with Ciprofloxacin Bayer (oral, intravenous, and sequential therapy) sorted by categories of frequency are listed below. The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin.

System Organ Class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1 000 to < 1/100	**Rare** ≥ 1/10 000 to < 1/1 000	**Very Rare** < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Infections and Infestations		Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4)		
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (life-threatening) (see section 4.4) Serum sickness-like reaction	
Metabolism and Nutrition Disorders		Anorexia	Hyperglycaemia		
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression Hallucinations	Psychotic reactions (see section 4.4)	

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	Frequency not known (cannot be estimated from available data)
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (see section 4.4) Vertigo	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension	Peripheral neuropathy (see section 4.4)
Eye Disorders			Visual disturbances	Visual colour distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss / Hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia, QT prolongation, torsades de pointes *
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Cholestatic icterus Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)	

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	Frequency not known (cannot be estimated from available data)
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions (see section 4.4)	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	
Musculoskeletal, Connective Tissue and Bone Disorders		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) (see section 4.4) Exacerbation of symptoms of myasthenia gravis (see section 4.4)	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria (see section 4.4) Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions		Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Prothrombin level abnormal Increased amylase		

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see section 4.4).

Paediatric patients

The incidence of arthropathy, mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see section 4.4).

4.9 Overdose

An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.
Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has been reported.

Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated. Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02

Mechanism of action:

As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

PK/PD relationship:

Efficacy mainly depends on the relation between the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

Mechanism of resistance:

In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.
Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All *in-vitro* mechanisms of resistance are commonly observed in clinical isolates.
Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to ciprofloxacin. Plasmid-mediated resistance encoded by qnr-genes has been reported.

Spectrum of antibacterial activity:

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

Microorganisms	Susceptible	Resistant
Enterobacteria	S ≤ 0.5 mg/L	R > 1 mg/L
Pseudomonas	S ≤ 0.5 mg/L	R > 1 mg/L
Acinetobacter	S ≤ 1 mg/L	R > 1 mg/L
Staphylococcus spp.[1]	S ≤ 1 mg/L	R > 1 mg/L

Haemophilus influenzae and *Moraxella catarrhalis*	S ≤ 0.5 mg/L	R > 0.5 mg/L
Neisseria gonorrhoeae	S ≤ 0.03 mg/L	R > 0.06 mg/L
Neisseria meningitidis	S ≤ 0.03 mg/L	R > 0.06 mg/L
Non-species-related breakpoints *****	S ≤ 0.5 mg/L	R > 1 mg/L

1 *Staphylococcus* spp. - breakpoints for ciprofloxacin relate to high dose therapy.

* Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Groupings of relevant species according to ciprofloxacin susceptibility (for *Streptococcus* species see section 4.4)

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms *Bacillus anthracis* (1)
Aerobic Gram-negative micro-organisms *Aeromonas* spp. *Brucella* spp. *Citrobacter koseri* *Francisella tularensis* *Haemophilus ducreyi* *Haemophilus influenzae* * *Legionella* spp. *Moraxella catarrhalis* * *Neisseria meningitidis* *Pasteurell*a spp. *Salmonella* spp.* *Shigella* spp.* *Vibrio* spp. *Yersinia pestis*
Anaerobic micro-organisms *Mobiluncus*
Other micro-organisms *Chlamydia trachomatis* ($) *Chlamydia pneumoniae* ($) *Mycoplasma hominis* ($) *Mycoplasma pneumoniae* ($)
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms *Enterococcus faecalis*($) *Staphylococcus* spp.*(2)
Aerobic Gram-negative micro-organisms *Acinetobacter baumannii*$^{+}$ *Burkholderia cepacia*$^{+*}$ *Campylobacter* spp.$^{+}$* *Citrobacter freundii** *Enterobacter aerogenes* *Enterobacter cloacae* * *Escherichia coli** *Klebsiella oxytoca* *Klebsiella pneumoniae** *Morganella morganii** *Neisseria gonorrhoeae** *Proteus mirabilis** *Proteus vulgaris** *Providencia* spp. *Pseudomonas aeruginosa** *Pseudomonas fluorescens* *Serratia marcescens**
Anaerobic micro-organisms *Peptostreptococcus* spp. *Propionibacterium acnes*

INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms *Actinomyces* *Enteroccus faecium* *Listeria monocytogenes*
Aerobic Gram-negative micro-organisms *Stenotrophomonas maltophilia*
Anaerobic micro-organisms *Excepted as listed above*
Other micro-organisms *Mycoplasma genitalium* *Ureaplasma urealitycum*
* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications. + Resistance rate ≥ 50% in one or more EU countries ($): Natural intermediate susceptibility in the absence of acquired mechanism of resistance (1): Studies have been conducted in experimental animal infections due to inhalations of *Bacillus anthracis* spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on *in-vitro* susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and /or international consensus documents regarding treatment of anthrax. (2): Methicillin-resistant *S. aureus* very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin tablets, ciprofloxacin is absorbed rapidly and extensively, mainly from the small intestine, reaching maximum serum concentrations 1-2 hours later.
Single doses of 100-750 mg produced dose-dependent maximum serum concentrations (C_{max}) between 0.56 and 3.7 mg/L. Serum concentrations increase proportionately with doses up to 1000 mg.
The absolute bioavailability is approximately 70-80%.
A 500 mg oral dose given every 12 hours has been shown to produce an area under the serum concentration-time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours.
The pharmacokinetics of ciprofloxacin 250 mg and 500 mg oral suspension in single-dose sachets are similar to those of tablets.

Distribution

Pprotein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Metabolism

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). The metabolites display *in-vitro* antimicrobial activity but to a lower degree than the parent compound.
Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally. The serum elimination half-life in subjects with normal renal function is approximately 4-7 hours.

Excretion of ciprofloxacin (% of dose)		
	Oral Administration	
	Urine	**Faeces**
Ciprofloxacin	44.7	25.0
Metabolites (M1-M4)	11.3	7.5

Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half lives of ciprofloxacin of up to 12 h.

Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Paediatric patients

The pharmacokinetic data in paediatric patients are limited.

In a study in children C_{max} and AUC were not age-dependent (above one year of age). No notable increase in C_{max} and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C_{max} was 6.1 mg/L (range 4.6-8.3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.7-11.8 mg/L) for children between 1 and 5 years of age. The AUC values were 17.4 mg*h/L (range 11.8-32.0 mg*h/L) and 16.5 mg*h/L (range 11.0-23.8 mg*h/L) in the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4-5 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction.
Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/ photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin *in-vitro* and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability:
As reported for other gyrase inhibitors, ciprofloxacin causes damage to the large weight-bearing joints in immature animals. The extent of the cartilage damage varies according to age, species and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs, ciprofloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal and other handling

Take the prescribed amount of sachets. Shake the sachet applying slight pressure to the walls. Then tear the sachet open as indicated and take the contents directly.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally.]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally.]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally.]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 50 mg/mL granules and solvent for oral suspension
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules and solvent for oral suspension
[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The Ciprofloxacin Bayer 50 mg/mL oral suspension is indicated for the treatment of the following infections (see sections 4.4 and 5.1). Special attention should be paid to available information on resistance to ciprofloxacin before commencing therapy.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Adults

- Lower respiratory tract infections due to Gram-negative bacteria
  - exacerbations of chronic obstructive pulmonary disease
  - broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
  - pneumonia
- Chronic suppurative otitis media
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
- Urinary tract infections
- Gonococcal uretritis and cervicitis
- Epididymo-orchitis including cases due to *Neisseria gonorrhoeae*
- Pelvic inflammatory disease including cases due to *Neisseria gonorrhoeae*

In the above genital tract infections when thought or known to be due to *Neisseria gonorrhoeae* it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility based on laboratory testing.

- Infections of the gastro-intestinal tract (e.g. travellers' diarrhoea)
- Intra-abdominal infections
- Infections of the skin and soft tissue caused by Gram-negative bacteria

- Malignant external otitis
- Infections of the bones and joints
- Treatment of infections in neutropenic patients
- Prophylaxis of infections in neutropenic patients
- Prophylaxis of invasive infections due to *Neisseria meningitidis*
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Children and adolescents

- Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*
- Complicated urinary tract infections and pyelonephritis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to be necessary.

Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents (see sections 4.4 and 5.1).

4.2 Posology and method of administration

The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to ciprofloxacin of the causative organism(s), the renal function of the patient and, in children and adolescents the body weight.
The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course.
Treatment of infections due to certain bacteria (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* or *Staphylococci*) may require higher ciprofloxacin doses and co-administration with other appropriate antibacterial agents.

Treatment of some infections (e.g. pelvic inflammatory disease, intra-abdominal infections, infections in neutropenic patients and infections of bones and joints) may require co-administration with other appropriate antibacterial agents depending on the pathogens involved.

Adults

Indications	**Daily dose in mg**	**Daily dose in mL (Number of 5-mL measuring spoonfuls)**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Infections of the lower respiratory tract	500 mg twice daily to 750 mg twice daily	10 mL twice daily to 15 mL twice daily (two 5-mL measuring spoonfuls twice daily up to three 5-mL measuring spoonfuls twice daily)	7 to 14 days

Indications		**Daily dose in mg**	**Daily dose in mL (Number of 5-mL measuring spoonfuls)**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	500 mg twice daily to 750 mg twice daily	10 mL twice daily to 15 mL twice daily (two 5-mL measuring spoonfuls twice daily up to three 5-mL measuring spoonfuls twice daily)	7 to 14 days
	Chronic suppurative otitis media	500 mg twice daily to 750 mg twice daily	10 mL twice daily to 15 mL twice daily (two 5-mL measuring spoonfuls twice daily up to three 5-mL measuring spoonfuls twice daily)	7 to 14 days
	Malignant external otitis	750 mg twice daily	15 mL twice daily (three 5-mL measuring spoonfuls twice daily)	28 days up to 3 months
Urinary tract infections	Uncomplicated cystitis	250 mg twice daily to 500 mg twice daily	5-mL twice daily to 10 mL twice daily (one 5-mL measuring spoonful twice daily up to two 5-mL measuring spoonfuls twice daily)	3 days
		In pre-menopausal women, 500 mg single dose may be used corresponding to 10 mL single dose = two 5-mL measuring spoonfuls as a single dose		
	Complicated cystitis, Uncomplicated pyelonephritis	500 mg twice daily	10 mL twice daily (two 5-mL measuring spoonfuls twice daily)	7 days
	Complicated pyelonephritis	500 mg twice daily to 750 mg twice daily	10 mL twice daily to 15-mL twice daily (two 5-mL measuring spoonfuls twice daily up to three 5-mL measuring spoonfuls twice daily)	at least 10 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Prostatitis	500 mg twice daily to 750 mg twice daily	10 mL twice daily to 15-mL twice daily (two 5-mL measuring spoonfuls twice daily up to three 5-mL measuring spoonfuls twice daily)	2 to 4 weeks (acute) to 4 to 6 weeks (chronic)

Indications		**Daily dose in mg**	**Daily dose in mL (Number of 5-mL measuring spoonfuls)**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Genital tract infections	Gonococcal uretritis and cervicitis	500 mg as a single dose	10 mL as a single dose corresponding to two 5-mL measuring spoonfuls as a single dose	1 day (single dose)
	Epididymo-orchitis and pelvic inflammatory diseases	500 mg twice daily to 750 mg twice daily	10 mL twice daily to 15-mL twice daily (two 5-mL measuring spoonfuls twice daily up to three 5-mL measuring spoonfuls twice daily)	at least 14 days
Infections of the gastro-intestinal tract and intra-abdominal infections	Diarrhoea caused by bacterial pathogens including *Shigella* spp. other than *Shigella dysenteriae* type 1 and empirical treatment of severe travellers' diarrhoea	500 mg twice daily	10 mL twice daily (two 5-mL measuring spoonfuls twice daily)	1 day
	Diarrhoea caused by *Shigella dysenteriae* type 1	500 mg twice daily	10 mL twice daily (two 5-mL measuring spoonfuls twice daily)	5 days
	Diarrhoea caused by *Vibrio cholerae*	500 mg twice daily	10 mL twice daily (two 5-mL measuring spoonfuls twice daily)	3 days
	Typhoid fever	500 mg twice daily	10 mL twice daily (two 5-mL measuring spoonfuls twice daily)	7 days
	Intra-abdominal infections due to Gram-negative bacteria	500 mg twice daily to 750 mg twice daily	10 mL twice daily to 15-mL twice daily (two 5-mL measuring spoonfuls twice daily up to three 5-mL measuring spoonfuls twice daily)	5 to 14 days

Indications	Daily dose in mg	Daily dose in mL (Number of 5-mL measuring spoonfuls)	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Infections of the skin and soft tissue	500 mg twice daily to 750 mg twice daily	10 mL twice daily to 15-mL twice daily (two 5-mL measuring spoonfuls twice daily up to three 5-mL measuring spoonfuls twice daily)	7 to 14 days
Bone and joint infections	500 mg twice daily to 750 mg twice daily	10 mL twice daily to 15-mL twice daily (two 5-mL measuring spoonfuls twice daily up to three 5-mL measuring spoonfuls twice daily)	max. of 3 months
Treatment of infections or prophylaxis of infections in neutropenic patients Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance.	500 mg twice daily to 750 mg twice daily	10 mL twice daily to 15-mL twice daily (two 5-mL measuring spoonfuls twice daily up to three 5-mL measuring spoonfuls twice daily)	Therapy should be continued over the entire period of neutropenia
Prophylaxis of invasive infections due to *Neisseria meningitidis*	500 mg as a single dose	10 mL as a single dose corresponding to two 5-mL measuring spoonfuls as a single dose	1 day (single dose)
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure.	500 mg twice daily	10 mL twice daily (two 5-mL measuring spoonfuls twice daily)	60 days from the confirmation of *Bacillus anthracis* exposure

Children and adolescents

Indications	Daily dose in mg and in mL	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Cystic fibrosis	20 mg/kg body weight twice daily with a maximum of 750 mg per dose, corresponding to a 0.4 mL/kg body weight twice daily with a maximum of 15-mL per dose	10 to 14 days

Indications	Daily dose in mg and in mL	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Complicated urinary tract infections and pyelonephritis	10 mg/kg body weight twice daily to 20 mg/kg body weight twice daily with a maximum of 750 mg per dose, corresponding to a 0.2 mL/kg body weight twice daily to 0.4 mL/kg body weight twice daily with a maximum of 15-mL per dose	10 to 21 days
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure.	10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 500 mg per dose, corresponding to a 0.2 mL/kg body weight twice daily to 0.3 mL/kg body weight twice daily with a maximum of 10 mL per dose	60 days from the confirmation of *Bacillus anthracis* exposure
Other severe infections	20 mg/kg body weight twice daily with a maximum of 750 mg per dose, corresponding to a 0.4 mL/kg body weight twice daily with a maximum of 15-mL per dose	According to the type of infections

Geriatric patients

Geriatric patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.

Renal and hepatic impairment

Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance [mL/min/ 1.73 m²]	Serum Creatinine [µmol/L]	Oral Dose [mg]
> 60	< 124	See Usual Dosage.
30-60	124 to 168	250-500 mg every 12 h
< 30	> 169	250-500 mg every 24 h
Patients on haemodialysis	> 169	250-500 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	250-500 mg every 24 h

In patients with impaired liver function no dose adjustment is required.

Dosing in children with impaired renal and/or hepatic function has not been studied.

Method of administration

Oral suspension can be taken independent of mealtimes.

If taken on an empty stomach, the active substance is absorbed more rapidly. Ciprofloxacin should not be taken with dairy products (e.g. milk, yoghurt) or mineral-fortified fruit juice (e.g. calcium-fortified orange juice) (see section 4.5).

In severe cases or if the patient is unable to take oral suspension (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

Appearance of the reconstituted product:

The reconstituted product is a white to slightly yellowish suspension with strawberry odour. Occasionally the suspension may contain yellow-orange droplets and globular particles.

½ measuring spoonful (approx 2.5-mL suspension) provides approx. 125 mg ciprofloxacin.
1 measuring spoonful (approx 5.0 mL suspension) provides approx. 250 mg ciprofloxacin.

Always use the graduated measuring spoon to obtain the exact dose for administering the suspension. No additions should be made to the mixed final ciprofloxacin suspension.

4.3 Contraindications

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients (see section 6.1).

- Concomitant administration of ciprofloxacin and tizanidine (see section 4.5).

4.4 Special warnings and precautions for use

Severe infections and mixed infections with Gram-positive and anaerobic pathogens
Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections ciprofloxacin must be co-administered with other appropriate antibacterial agents.

Streptococcal Infections (including Streptococcus pneumoniae)
Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Genital tract infections
Epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*. Ciprofloxacin should be co-administered with another appropriate antibacterial agent unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Intra-abdominal infections
There are limited data on the efficacy of ciprofloxacin in the treatment of post-surgical intra-abdominal infections.

Travellers' diarrhoea
The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited.

Infections of the bones and joints
Ciprofloxacin should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation.

Inhalational anthrax
Use in humans is based on *in-vitro* susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and /or international consensus documents regarding the treatment of anthrax.

Children and adolescents
The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. Safety data from a randomised double-blind study on ciprofloxacin use in children (ciprofloxacin: n=335, mean age = 6.3 years; comparators: n=349, mean age = 6.2 years; age range = 1 to 17 years) revealed an incidence of suspected drug-related arthropathy (discerned from joint-related clinical signs and symptoms) by Day +42 of 7.2% and 4.6%. Respectively, an incidence of drug-related arthropathy by 1-year follow-up was 9.0% and 5.7%. The increase of suspected drug-related arthropathy cases over time was not statistically significant between groups. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue.

Broncho-pulmonary infections in cystic fibrosis
Clinical trials have included children and adolescents aged 5-17 years. More limited experience is available in treating children between 1 and 5 years of age.

Complicated urinary tract infections and pyelonephritis
Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.
Clinical trials have included children and adolescents aged 1-17 years.

Other specific severe infections
Other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify a ciprofloxacin use.
The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with these infections.

Hypersensitivity
Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose (see section 4.8) and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.

Musculoskeletal System
Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.
Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, as soon as the first 48 hours of treatment. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids (see section 4.8).

At any sign of tendinitis (e.g. painful swelling, inflammation), ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected limb at rest.
Ciprofloxacin should be used with caution in patients with myasthenia gravis (see section 4.8).

Photosensitivity
Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking ciprofloxacin should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment (see section 4.8).

Central Nervous System
Quinolones are known to trigger seizures or lower the seizure threshold. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued (see section 4.8). Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to self-endangering behaviour. In these cases, ciprofloxacin should be discontinued.
Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving ciprofloxacin. Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see section 4.8).

Cardiac disorders
Since ciprofloxacin is associated with cases of QT prolongation (see section 4.8), caution should be exercised when treating patients at risk for torsades de pointes arrhythmia.

Gastrointestinal System
The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment (see section 4.8). In such cases, ciprofloxacin should immediately be discontinued, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.

Renal and urinary system
Crystalluria related to the use of ciprofloxacin has been reported (see section 4.8). Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

Hepatobiliary system
Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see section 4.8). In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued.

Glucose-6-phosphate dehydrogenase deficiency
Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.

Resistance
During or following a course of treatment with ciprofloxacin bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas* species.

Cytochrome P450
Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, ropinirole, tizanidine). Co-administration of ciprofloxacin and tizanidine is contra-indicated. Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5).

Methotrexate
The concomitant use of ciprofloxacin with methotrexate is not recommended (see section 4.5).

Interaction with tests
The *in-vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients currently taking ciprofloxacin.

Sucrose Load
As the oral suspension contains sucrose, it should not be used in patients with fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase deficiency.
As Ciprofloxacin Bayer 50 mg/mL suspension contains 1.4 g sucrose per 5-mL measuring spoonful, this has to be taken into consideration in terms of daily intake.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other products on ciprofloxacin:

Chelation Complex Formation

The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing drugs and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of ciprofloxacin. Consequently, ciprofloxacin should be administered either 1-2 hours before or at least 4 hours after these preparations. The restriction does not apply to antacids belonging to the class of H2 receptor blockers.

Food and Dairy Products

Dietary calcium as part of a meal does not significantly affect absorption. However, the concurrent administration of dairy products or mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice) with ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced.

Probenecid

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.

Effects of ciprofloxacin on other medicinal products:

Tizanidine

Tizanidine must not be administered together with ciprofloxacin (see section 4.3). In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

Theophylline

Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary (see section 4.4).

Other xanthine derivatives

On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivatives were reported.

Phenytoin

Simultaneous administration of ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin such that monitoring of drug levels is recommended.

Oral anti-coagulants

Simultaneous administration of ciprofloxacin with warfarin may augment its anti-coagulant effects. There have been many reports of increases in oral anti-coagulant activity in patients receiving antibacterial agents, including fluoroquinolones. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the fluoroquinolone to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anti-coagulant agent.

Ropinirole

It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, results in an increase of C_{max} and AUC of ropinirole by 60% and 84%, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin (see section 4.4).

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy

The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the

drug could cause damage to articular cartilage in the human immature organism / foetus (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

Lactation
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are nausea and diarrhoea.

ADRs derived from clinical studies and post-marketing surveillance with Ciprofloxacin Bayer (oral, intravenous, and sequential therapy) sorted by categories of frequency are listed below. The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin.

System Organ Class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1 000 to < 1/100	**Rare** ≥ 1/10 000 to < 1/1 000	**Very Rare** < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Infections and Infestations		Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4)		
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (life-threatening) (see section 4.4) Serum sickness-like reaction	
Metabolism and Nutrition Disorders		Anorexia	Hyperglycaemia		

System Organ Class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1 000 to < 1/100	**Rare** ≥ 1/10 000 to < 1/1 000	**Very Rare** < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression Hallucinations	Psychotic reactions (see section 4.4)	
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (see section 4.4) Vertigo	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension	Peripheral neuropathy (see section 4.4)
Eye Disorders			Visual disturbances	Visual colour distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss / Hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia, QT prolongation, torsades de pointes *
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Cholestatic icterus Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)	

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	Frequency not known (cannot be estimated from available data)
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions (see section 4.4)	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	
Musculoskeletal, Connective Tissue and Bone Disorders		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) (see section 4.4) Exacerbation of symptoms of myasthenia gravis (see section 4.4)	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria (see section 4.4) Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions		Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Prothrombin level abnormal Increased amylase		

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see section 4.4).

Paediatric patients

The incidence of arthropathy, mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see section 4.4).

4.9 Overdose

An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.
Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has been reported.

Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated. Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02

Mechanism of action:

As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

PK/PD relationship:

Efficacy mainly depends on the relation between the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

Mechanism of resistance:

In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.
Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All *in-vitro* mechanisms of resistance are commonly observed in clinical isolates.
Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to ciprofloxacin.
Plasmid-mediated resistance encoded by qnr-genes has been reported.

Spectrum of antibacterial activity:

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

Microorganisms	Susceptible	Resistant
Enterobacteria	S ≤ 0.5 mg/L	R > 1 mg/L
Pseudomonas	S ≤ 0.5 mg/L	R > 1 mg/L
Acinetobacter	S ≤ 1 mg/L	R > 1 mg/L

Staphylococcus spp.[1]	S ≤ 1 mg/L	R > 1 mg/L
Haemophilus influenzae and *Moraxella catarrhalis*	S ≤ 0.5 mg/L	R > 0.5 mg/L
Neisseria gonorrhoeae	S ≤ 0.03 mg/L	R > 0.06 mg/L
Neisseria meningitidis	S ≤ 0.03 mg/L	R > 0.06 mg/L
Non-species-related breakpoints *****	S ≤ 0.5 mg/L	R > 1 mg/L

1 *Staphylococcus* spp. – breakpoints for ciprofloxacin relate to high dose therapy.

* Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Groupings of relevant species according to ciprofloxacin susceptibility (for *Streptococcus* species see section 4.4)

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms *Bacillus anthracis* (1)
Aerobic Gram-negative micro-organisms *Aeromonas* spp. *Brucella* spp. *Citrobacter koseri* *Francisella tularensis* *Haemophilus ducreyi* *Haemophilus influenzae* * *Legionella* spp. *Moraxella catarrhalis* * *Neisseria meningitidis* *Pasteurella* spp. *Salmonella* spp.* *Shigella* spp.* *Vibrio* spp. *Yersinia pestis*
Anaerobic micro-organisms *Mobiluncus*
Other micro-organisms *Chlamydia trachomatis* ($) *Chlamydia pneumoniae* ($) *Mycoplasma hominis* ($) *Mycoplasma pneumoniae* ($)
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* ($) *Staphylococcus* spp.*(2)

Aerobic Gram-negative micro-organisms *Acinetobacter baumannii*[+] *Burkholderia cepacia*[+*] *Campylobacter* spp.[+]* *Citrobacter freundii** *Enterobacter aerogenes* *Enterobacter cloacae ** *Escherichia coli** *Klebsiella oxytoca* *Klebsiella pneumoniae** *Morganella morganii** *Neisseria gonorrhoeae** *Proteus mirabilis** *Proteus vulgaris** *Providencia* spp. *Pseudomonas aeruginosa** *Pseudomonas fluorescens* *Serratia marcescens**
Anaerobic micro-organisms *Peptostreptococcus* spp. *Propionibacterium acnes*
INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms *Actinomyces* *Enteroccus faecium* *Listeria monocytogenes*
Aerobic Gram-negative micro-organisms *Stenotrophomonas maltophilia*
Anaerobic micro-organisms Excepted as listed above
Other micro-organisms *Mycoplasma genitalium* *Ureaplasma urealitycum*
* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications. [+] Resistance rate ≥ 50% in one or more EU countries. ($): Natural intermediate susceptibility in the absence of acquired mechanism of resistance (1): Studies have been conducted in experimental animal infections due to inhalations of *Bacillus anthracis* spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on *in-vitro* susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and /or international consensus documents regarding treatment of anthrax. (2): Methicillin-resistant *S. aureus* very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin tablets, ciprofloxacin is absorbed rapidly and extensively, mainly from the small intestine, reaching maximum serum concentrations 1-2 hours later.
Single doses of 100-750 mg produced dose-dependent maximum serum concentrations (C_{max}) between 0.56 and 3.7 mg/L. Serum concentrations increase proportionately with doses up to 1000 mg.
The absolute bioavailability is approximately 70-80%.
A 500 mg oral dose given every 12 hours has been shown to produce an area under the serum concentration-time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours.
The pharmacokinetics of ciprofloxacin oral suspension 50 mg/mL and 100 mg/mL are similar to those of tablets.

Distribution

Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionized form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Metabolism

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). The metabolites display *in-vitro* antimicrobial activity but to a lower degree than the parent compound.
Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally. The serum elimination half-life in subjects with normal renal function is approximately 4-7 hours.

Excretion of ciprofloxacin (% of dose)		
	Oral Administration	
	Urine	**Faeces**
Ciprofloxacin	44.7	25.0
Metabolites (M1-M4)	11.3	7.5

Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half lives of ciprofloxacin of up to 12 h.

Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Paediatric patients

The pharmacokinetic data in paediatric patients are limited.

In a study in children C_{max} and AUC were not age-dependent (above one year of age). No notable increase in Cmax and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C_{max} was 6.1 mg/L (range 4.6-8.3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.7-11.8 mg/L) for children between 1 and 5 years of age. The AUC values were 17.4 mg*h/L (range 11.8-32.0 mg*h/L) and 16.5 mg*h/L (range 11.0-23.8 mg*h/L) in the respective age groups. These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4-5 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction.
Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/ photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin *in-vitro* and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability:
As reported for other gyrase inhibitors, ciprofloxacin causes damage to the large weight-bearing joints in immature animals. The extent of the cartilage damage varies according to age, species and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs, ciprofloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal and other handling

The small bottle contains the active substance and the large bottle contains the solvent. Open both bottles.

Reconstitution

Press down according to instructions on the cap while turning to the left. Pour the granules completely into the large bottle with the suspension fluid.
Do not pour water into the suspension!
Reclose the large bottle properly according to the instructions on the cap and shake vigorously for about 15 seconds. The ready-to-use suspension is now finished.
Taking the Ready-to-Use Suspension

Take the prescribed amount of suspension by using the measuring spoon. Do not chew the granules present in the suspension, simply swallow them. A drink of water may be taken afterwards. Reclose the bottle properly after use according to the instructions on the cap. The ready-to-use suspension is stable for 14 days when stored in a refrigerator or at ambient temperatures below 30°C. After treatment has been completed, it should not be reused. **Shake vigorously each time before use for approximately 15 seconds.**
The graduated measuring spoon with the markings 1/2 is equivalent to 2.6 mL containing 2.5-mL of final suspension and 1/1 is equivalent to 5.2 mL containing 5.0 mL of final suspension. The graduated measuring spoon must be used for measuring the required prescribed amount of Ciprofloxacin oral suspension 50 mg/mL.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally.]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally.]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally.]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 100 mg/mL granules and solvent for oral suspension
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules and solvent for oral suspension
[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The Ciprofloxacin Bayer 100 mg/mL oral suspension is indicated for the treatment of the following infections (see sections 4.4 and 5.1). Special attention should be paid to available information on resistance to ciprofloxacin before commencing therapy.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Adults

- Lower respiratory tract infections due to Gram-negative bacteria
  - exacerbations of chronic obstructive pulmonary disease
  - broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
  - pneumonia
- Chronic suppurative otitis media
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
- Urinary tract infections
- Gonococcal uretritis and cervicitis
- Epididymo-orchitis including cases due to *Neisseria gonorrhoeae*
- Pelvic inflammatory disease including cases due to *Neisseria gonorrhoeae*

In the above genital tract infections when thought or known to be due to *Neisseria gonorrhoeae* it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility based on laboratory testing.

- Infections of the gastro-intestinal tract (e.g. travellers' diarrhoea)
- Intra-abdominal infections
- Infections of the skin and soft tissue caused by Gram-negative bacteria

- Malignant external otitis
- Infections of the bones and joints
- Treatment of infections in neutropenic patients
- Prophylaxis of infections in neutropenic patients
- Prophylaxis of invasive infections due to *Neisseria meningitidis*
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Children and adolescents

- Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*
- Complicated urinary tract infections and pyelonephritis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to be necessary.

Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents (see sections 4.4 and 5.1).

4.2 Posology and method of administration

The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to ciprofloxacin of the causative organism(s), the renal function of the patient and, in children and adolescents the body weight.
The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course.
Treatment of infections due to certain bacteria (e.g. *Pseudomonas aeruginosa, Acinetobacter* or *Staphylococci*) may require higher ciprofloxacin doses and co-administration with other appropriate antibacterial agents.

Treatment of some infections (e.g. pelvic inflammatory disease, intra-abdominal infections, infections in neutropenic patients and infections of bones and joints) may require co-administration with other appropriate antibacterial agents depending on the pathogens involved.

Adults

Indications	**Daily dose in mg**	**Daily dose in mL (Number of 5-mL measuring spoonfuls)**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Infections of the lower respiratory tract	500 mg twice daily to 750 mg twice daily	5 mL twice daily to 7.5 mL twice daily (one 5-mL measuring spoonful twice daily up to one and a half 5-mL measuring spoonfuls twice daily)	7 to 14 days

Indications		**Daily dose in mg**	**Daily dose in mL (Number of 5-mL measuring spoonfuls)**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	500 mg twice daily to 750 mg twice daily	5 mL twice daily to 7.5 mL twice daily (one 5-mL measuring spoonful twice daily up to one and a half 5-mL measuring spoonfuls twice daily)	7 to 14 days
	Chronic suppurative otitis media	500 mg twice daily to 750 mg twice daily	5 mL twice daily to 7.5 mL twice daily (one 5-mL measuring spoonful twice daily up to one and a half 5-mL measuring spoonfuls twice daily)	7 to 14 days
	Malignant external otitis	750 mg twice daily	7.5 mL twice daily (one and a half 5-mL measuring spoonfuls twice daily)	28 days up to 3 months
Urinary tract infections	Uncomplicated cystitis	250 mg twice daily to 500 mg twice daily	2.5 mL twice daily to 5 mL twice daily (half 5-mL measuring spoonful twice daily up to one 5-mL measuring spoonful twice daily)	3 days
		In pre-menopausal women, 500 mg single dose may be used corresponding to 5 mL single dose = one 5-mL measuring spoonful as a single dose		
	Complicated cystitis, Uncomplicated pyelonephritis	500 mg twice daily	5 mL twice daily (one 5-mL measuring spoonful twice daily)	7 days
	Complicated pyelonephritis	500 mg twice daily to 750 mg twice daily	5 mL twice daily to 7.5 mL twice daily (one 5-mL measuring spoonful twice daily up to one and a half 5-mL measuring spoonfuls twice daily)	at least 10 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Prostatitis	500 mg twice daily to 750 mg twice daily	5 mL twice daily to 7.5 mL twice daily (one 5-mL measuring spoonful twice daily up to one and a half 5-mL measuring spoonfuls twice daily)	2 to 4 weeks (acute) to 4 to 6 weeks (chronic)

Indications		**Daily dose in mg**	**Daily dose in mL (Number of 5-mL measuring spoonfuls)**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Genital tract infections	Gonococcal uretritis and cervicitis	500 mg as a single dose	5 mL as a single dose corresponding to one 5-mL measuring spoonful as a single dose	1 day (single dose)
	Epididymo-orchitis and pelvic inflammatory diseases	500 mg twice daily to 750 mg twice daily	5 mL twice daily to 7.5 mL twice daily (one 5-mL measuring spoonful twice daily up to one and a half 5-mL measuring spoonfuls twice daily)	at least 14 days
Infections of the gastro-intestinal tract and intra-abdominal infections	Diarrhoea caused by bacterial pathogens including *Shigella* spp. other than *Shigella dysenteriae* type 1 and empirical treatment of severe travellers' diarrhoea	500 mg twice daily	5 mL twice daily (one 5-mL measuring spoonful twice daily)	1 day
	Diarrhoea caused by *Shigella dysenteriae* type 1	500 mg twice daily	5 mL twice daily (one 5-mL measuring spoonful twice daily)	5 days
	Diarrhoea caused by *Vibrio cholerae*	500 mg twice daily	5 mL twice daily (one 5-mL measuring spoonful twice daily)	3 days
	Typhoid fever	500 mg twice daily	5 mL twice daily (one 5-mL measuring spoonful twice daily)	7 days
	Intra-abdominal infections due to Gram-negative bacteria	500 mg twice daily to 750 mg twice daily	5 mL twice daily to 7.5 mL twice daily (one 5-mL measuring spoonful twice daily up to one and a half 5-mL measuring spoonfuls twice daily)	5 to 14 days

Indications	Daily dose in mg	Daily dose in mL (Number of 5-mL measuring spoonfuls)	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Infections of the skin and soft tissue	500 mg twice daily to 750 mg twice daily	5 mL twice daily to 7.5 mL twice daily (one 5-mL measuring spoonful twice daily up to one and a half 5-mL measuring spoonfuls twice daily)	7 to 14 days
Bone and joint infections	500 mg twice daily to 750 mg twice daily	5 mL twice daily to 7.5 mL twice daily (one 5-mL measuring spoonful twice daily up to one and a half 5-mL measuring spoonfuls twice daily)	max. of 3 months
Treatment of infections or prophylaxis of infections in neutropenic patients Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance.	500 mg twice daily to 750 mg twice daily	5 mL twice daily to 7.5 mL twice daily (one 5-mL measuring spoonful twice daily up to one and a half 5-mL measuring spoonfuls twice daily)	Therapy should be continued over the entire period of neutropenia
Prophylaxis of invasive infections due to *Neisseria meningitidis*	500 mg as a single dose	5 mL as a single dose corresponding to one 5-mL measuring spoonful as a single dose	1 day (single dose)
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure.	500 mg twice daily	5 mL twice daily (one 5-mL measuring spoonful twice daily)	60 days from the confirmation of *Bacillus anthracis* exposure

Children and adolescents

Indications	Daily dose in mg and in mL	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Cystic fibrosis	20 mg/kg body weight twice daily with a maximum of 750 mg per dose, corresponding to a 0.2 mL/kg body weight twice daily with a maximum of 7.5 mL per dose	10 to 14 days

Indications	Daily dose in mg and in mL	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Complicated urinary tract infections and pyelonephritis	10 mg/kg body weight twice daily to 20 mg/kg body weight twice daily with a maximum of 750 mg per dose, corresponding to a 0.1 mL/kg body weight twice daily to 0.2 mL/kg body weight twice daily with a maximum of 7.5 mL per dose	10 to 21 days
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure.	10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 500 mg per dose, corresponding to a 0.1 mL/kg body weight twice daily to 0.15 mL/kg body weight twice daily with a maximum of 5 mL per dose	60 days from the confirmation of *Bacillus anthracis* exposure
Other severe infections	20 mg/kg body weight twice daily with a maximum of 750 mg per dose, corresponding to a 0.2 mL/kg body weight twice daily with a maximum of 7.5 mL per dose	According to the type of infections

Geriatric patients

Geriatric patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.

Renal and hepatic impairment

Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance [mL/min/ 1.73 m²]	Serum Creatinine [µmol/L]	Oral Dose [mg]
> 60	< 124	See Usual Dosage.
30-60	124 to 168	250-500 mg every 12 h
< 30	> 169	250-500 mg every 24 h
Patients on haemodialysis	> 169	250-500 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	250-500 mg every 24 h

In patients with impaired liver function no dose adjustment is required.

Dosing in children with impaired renal and/or hepatic function has not been studied.

Method of administration

Oral suspension can be taken independent of mealtimes.

If taken on an empty stomach, the active substance is absorbed more rapidly. Ciprofloxacin should not be taken with dairy products (e.g. milk, yoghurt) or mineral-fortified fruit juice (e.g. calcium-fortified orange juice) (see section 4.5).

In severe cases or if the patient is unable to take oral suspension (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

Appearance of the reconstituted product:

The reconstituted product is a white to slightly yellowish suspension with strawberry odour. Occasionally the suspension may contain yellow-orange droplets and globular particles.

½ measuring spoonful (approx 2.5 mL suspension) provides approx. 250 mg ciprofloxacin.
1 measuring spoonful (approx 5.0 mL suspension) provides approx. 500 mg ciprofloxacin.

Always use the graduated measuring spoon to obtain the exact dose for administering the suspension. No additions should be made to the mixed final ciprofloxacin suspension.

4.3 Contraindications

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients (see section 6.1).

- Concomitant administration of ciprofloxacin and tizanidine (see section 4.5).

4.4 Special warnings and precautions for use

Severe infections and mixed infections with Gram-positive and anaerobic pathogens
Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections ciprofloxacin must be co-administered with other appropriate antibacterial agents.

Streptococcal Infections (including Streptococcus pneumoniae)
Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Genital tract infections
Epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*. Ciprofloxacin should be co-administered with another appropriate antibacterial agent unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Intra-abdominal infections
There are limited data on the efficacy of ciprofloxacin in the treatment of post-surgical intra-abdominal infections.

Travellers' diarrhoea
The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited.

Infections of the bones and joints
Ciprofloxacin should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation.

Inhalational anthrax
Use in humans is based on *in-vitro* susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and /or international consensus documents regarding the treatment of anthrax.

Children and adolescents
The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. Safety data from a randomised double-blind study on ciprofloxacin use in children (ciprofloxacin: n=335, mean age = 6.3 years; comparators: n=349, mean age = 6.2 years; age range = 1 to 17 years) revealed an incidence of suspected drug-related arthropathy (discerned from joint-related clinical signs and symptoms) by Day +42 of 7.2% and 4.6%. Respectively, an incidence of drug-related arthropathy by 1-year follow-up was 9.0% and 5.7%. The increase of suspected drug-related arthropathy cases over time was not statistically significant between groups. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue.

Broncho-pulmonary infections in cystic fibrosis
Clinical trials have included children and adolescents aged 5-17 years. More limited experience is available in treating children between 1 and 5 years of age.

Complicated urinary tract infections and pyelonephritis
Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.
Clinical trials have included children and adolescents aged 1-17 years.

Other specific severe infections
Other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify a ciprofloxacin use.
The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with these infections.

Hypersensitivity
Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose (see section 4.8) and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.

Musculoskeletal System
Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.

Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, as soon as the first 48 hours of treatment. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids (see section 4.8).
At any sign of tendinitis (e.g. painful swelling, inflammation), ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected limb at rest.
Ciprofloxacin should be used with caution in patients with myasthenia gravis (see section 4.8).

Photosensitivity
Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking ciprofloxacin should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment (see section 4.8).

Central Nervous System
Quinolones are known to trigger seizures or lower the seizure threshold. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued (see section 4.8). Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to self-endangering behaviour. In these cases, ciprofloxacin should be discontinued.
Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving ciprofloxacin. Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see section 4.8).

Cardiac disorders
Since ciprofloxacin is associated with cases of QT prolongation (see section 4.8), caution should be exercised when treating patients at risk for torsades de pointes arrhythmia.

Gastrointestinal System
The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment (see section 4.8). In such cases, ciprofloxacin should immediately be discontinued, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.

Renal and urinary system
Crystalluria related to the use of ciprofloxacin has been reported (see section 4.8). Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

Hepatobiliary system
Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see section 4.8). In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued.

Glucose-6-phosphate dehydrogenase deficiency
Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.

Resistance
During or following a course of treatment with ciprofloxacin bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas* species.

Cytochrome P450
Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, ropinirole, tizanidine). Co-administration of ciprofloxacin and tizanidine is contra-indicated. Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5).

Methotrexate
The concomitant use of ciprofloxacin with methotrexate is not recommended (see section 4.5).

Interaction with tests
The *in-vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients currently taking ciprofloxacin.

Sucrose Load
As the oral suspension contains sucrose, it should not be used in patients with fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase deficiency**.**
As Ciprofloxacin Bayer 100 mg/mL suspension contains 1.3 g sucrose per 5-mL measuring spoonful, this has to be taken into consideration in terms of daily intake.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other products on ciprofloxacin:

Chelation Complex Formation

The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing drugs and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of ciprofloxacin. Consequently, ciprofloxacin should be administered either 1-2 hours before or at least 4 hours after these preparations. The restriction does not apply to antacids belonging to the class of H2 receptor blockers.

Food and Dairy Products

Dietary calcium as part of a meal does not significantly affect absorption. However, the concurrent administration of dairy products or mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice) with ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced.

Probenecid

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.

Effects of ciprofloxacin on other medicinal products:

Tizanidine

Tizanidine must not be administered together with ciprofloxacin (see section 4.3). In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

Theophylline

Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary (see section 4.4).

Other xanthine derivatives

On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivatives were reported.

Phenytoin

Simultaneous administration of ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin such that monitoring of drug levels is recommended.

Oral anti-coagulants

Simultaneous administration of ciprofloxacin with warfarin may augment its anti-coagulant effects. There have been many reports of increases in oral anti-coagulant activity in patients receiving antibacterial agents, including fluoroquinolones. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the fluoroquinolone to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anti-coagulant agent.

Ropinirole

It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, results in an increase of C_{max} and AUC of ropinirole by 60% and 84%, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin (see section 4.4).

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy

The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the

drug could cause damage to articular cartilage in the human immature organism / foetus (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

Lactation
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are nausea and diarrhoea.

ADRs derived from clinical studies and post-marketing surveillance with Ciprofloxacin Bayer (oral, intravenous, and sequential therapy) sorted by categories of frequency are listed below. The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin.

System Organ Class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1 000 to < 1/100	**Rare** ≥ 1/10 000 to < 1/1 000	**Very Rare** < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Infections and Infestations		Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4)		
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (life-threatening) (see section 4.4) Serum sickness-like reaction	
Metabolism and Nutrition Disorders		Anorexia	Hyperglycaemia		

System Organ Class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1 000 to < 1/100	**Rare** ≥ 1/10 000 to < 1/1 000	**Very Rare** < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression Hallucinations	Psychotic reactions (see section 4.4)	
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (see section 4.4) Vertigo	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension	Peripheral neuropathy (see section 4.4)
Eye Disorders			Visual disturbances	Visual colour distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss / Hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia, QT prolongation, torsades de pointes *
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Cholestatic icterus Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)	

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	Frequency not known (cannot be estimated from available data)
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions (see section 4.4)	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	
Musculoskeletal, Connective Tissue and Bone Disorders		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) (see section 4.4) Exacerbation of symptoms of myasthenia gravis (see section 4.4)	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria (see section 4.4) Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions		Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Prothrombin level abnormal Increased amylase		

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see section 4.4).

Paediatric patients

The incidence of arthropathy, mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see section 4.4).

4.9 Overdose

An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.
Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has been reported.

Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated. Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02

Mechanism of action:

As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

PK/PD relationship:

Efficacy mainly depends on the relation between the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

Mechanism of resistance:

In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.
Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All *in-vitro* mechanisms of resistance are commonly observed in clinical isolates.
Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to ciprofloxacin.
Plasmid-mediated resistance encoded by qnr-genes has been reported.

Spectrum of antibacterial activity:

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

Microorganisms	Susceptible	Resistant
Enterobacteria	S ≤ 0.5 mg/L	R > 1 mg/L
Pseudomonas	S ≤ 0.5 mg/L	R > 1 mg/L

Acinetobacter	S ≤ 1 mg/L	R > 1 mg/L
Staphylococcus spp.[1]	S ≤ 1 mg/L	R > 1 mg/L
Haemophilus influenzae and *Moraxella catarrhalis*	S ≤ 0.5 mg/L	R > 0.5 mg/L
Neisseria gonorrhoeae	S ≤ 0.03 mg/L	R > 0.06 mg/L
Neisseria meningitidis	S ≤ 0.03 mg/L	R > 0.06 mg/L
Non-species-related breakpoints *	S ≤ 0.5 mg/L	R > 1 mg/L

1 *Staphylococcus* spp. - breakpoints for ciprofloxacin relate to high dose therapy.

* Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Groupings of relevant species according to ciprofloxacin susceptibility (for *Streptococcus* species see section 4.4)

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms *Bacillus anthracis* (1)
Aerobic Gram-negative micro-organisms *Aeromonas* spp. *Brucella* spp. *Citrobacter koseri* *Francisella tularensis* *Haemophilus ducreyi* *Haemophilus influenzae* * *Legionella* spp. *Moraxella catarrhalis* * *Neisseria meningitidis* *Pasteurella* spp. *Salmonella* spp. * *Shigella* spp.* *Vibrio* spp. *Yersinia pestis*
Anaerobic micro-organisms *Mobiluncus*
Other micro-organisms *Chlamydia trachomatis ($)* *Chlamydia pneumoniae ($)* *Mycoplasma hominis ($)* *Mycoplasma pneumoniae ($)*
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* ($) *Staphylococcus* spp. *(2)

Aerobic Gram-negative micro-organisms *Acinetobacter baumannii*[+] *Burkholderia cepacia*[+*] *Campylobacter* spp.[+]* *Citrobacter freundii** *Enterobacter aerogenes* *Enterobacter cloacae** *Escherichia coli** *Klebsiella oxytoca* *Klebsiella pneumoniae** *Morganella morganii** *Neisseria gonorrhoeae ** *Proteus mirabilis** *Proteus vulgaris** *Providencia* spp. *Pseudomonas aeruginosa** *Pseudomonas fluorescens* *Serratia marcescens**
Anaerobic micro-organisms *Peptostreptococcus* spp. *Propionibacterium acnes*
INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms *Actinomyces* *Enteroccus faecium* *Listeria monocytogenes*
Aerobic Gram-negative micro-organisms *Stenotrophomonas maltophilia*
Anaerobic micro-organisms Excepted as listed above
Other micro-organisms *Mycoplasma genitalium* *Ureaplasma urealitycum*
* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications. + Resistance rate ≥ 50% in one or more EU countries. ($): Natural intermediate susceptibility in the absence of acquired mechanism of resistance (1): Studies have been conducted in experimental animal infections due to inhalations of *Bacillus anthracis* spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on *in-vitro* susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and /or international consensus documents regarding treatment of anthrax. (2): Methicillin-resistant *S. aureus* very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin tablets, ciprofloxacin is absorbed rapidly and extensively, mainly from the small intestine, reaching maximum serum concentrations 1-2 hours later.
Single doses of 100-750 mg produced dose-dependent maximum serum concentrations (C_{max}) between 0.56 and 3.7 mg/L. Serum concentrations increase proportionately with doses up to 1000 mg.
The absolute bioavailability is approximately 70-80%.
A 500 mg oral dose given every 12 hours has been shown to produce an area under the serum concentration-time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours.
The pharmacokinetics of ciprofloxacin oral suspension 50 mg/mL and 100 mg/mL are similar to those of tablets.

Distribution

Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionized form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Metabolism

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). The metabolites display *in-vitro* antimicrobial activity but to a lower degree than the parent compound.
Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally. The serum elimination half-life in subjects with normal renal function is approximately 4-7 hours.

Excretion of ciprofloxacin (% of dose)		
	Oral Administration	
	Urine	**Faeces**
Ciprofloxacin	44.7	25.0
Metabolites (M1-M4)	11.3	7.5

Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half lives of ciprofloxacin of up to 12 h.

Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Paediatric patients

The pharmacokinetic data in paediatric patients are limited.

In a study in children C_{max} and AUC were not age-dependent (above one year of age). No notable increase in C_{max} and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C_{max} was 6.1 mg/L (range 4.6-8.3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.7-11.8 mg/L) for children between 1 and 5 years of age. The AUC values were 17.4 mg*h/L (range 11.8-32.0 mg*h/L) and 16.5 mg*h/L (range 11.0-23.8 mg*h/L) in the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4-5 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction.
Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/ photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin *in-vitro* and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability:
As reported for other gyrase inhibitors, ciprofloxacin causes damage to the large weight-bearing joints in immature animals. The extent of the cartilage damage varies according to age, species and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs, ciprofloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal and other handling

The small bottle contains the active substance and the large bottle contains the solvent. Open both bottles.

Reconstitution

Press down according to instructions on the cap while turning to the left. Pour the granules completely into the large bottle with the suspension fluid.
Do not pour water into the suspension!
Reclose the large bottle properly according to the instructions on the cap and shake vigorously for about 15 seconds. The ready-to-use suspension is now finished.

Taking the Ready-to-Use Suspension

Take the prescribed amount of suspension by using the measuring spoon. Do not chew the granules present in the suspension, simply swallow them. A drink of water may be taken afterwards. Reclose the bottle properly after use according to the instructions on the cap. The ready-to-use suspension is stable for 14 days when stored in a refrigerator or at ambient temperatures below 30°C. After treatment has been completed, it should not be reused. **Shake vigorously each time before use for approximately 15 seconds.**
The graduated measuring spoon with the markings 1/2 is equivalent to 2.6 mL containing 2.5 mL of final suspension and 1/1 is equivalent to 5.2 mL containing 5.0 mL of final suspension. The graduated measuring spoon must be used for measuring the required prescribed amount of Ciprofloxacin oral suspension 100 mg/mL.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally.]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally.]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally.]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 200 mg/100 mL solution for infusion
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ciprofloxacin Bayer 200 mg/100 mL solution for infusion is indicated for the treatment of the following infections (see sections 4.4 and 5.1). Special attention should be paid to available information on resistance to ciprofloxacin before commencing therapy.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Adults

- Lower respiratory tract infections due to Gram-negative bacteria
  - exacerbations of chronic obstructive pulmonary disease
  - broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
  - pneumonia
- Chronic suppurative otitis media
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
- Urinary tract infections
- Epididymo-orchitis including cases due to *Neisseria gonorrhoeae*
- Pelvic inflammatory disease including cases due to *Neisseria gonorrhoeae*

In the above genital tract infections when thought or known to be due to *Neisseria gonorrhoeae* it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility based on laboratory testing.

- Infections of the gastro-intestinal tract (e.g. travellers` diarrhoea)
- Intra-abdominal infections
- Infections of the skin and soft tissue caused by Gram-negative bacteria
- Malignant external otitis

- Infections of the bones and joints
- Treatment of infections in neutropenic patients
- Prophylaxis of infections in neutropenic patients
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Children and adolescents

- Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*
- Complicated urinary tract infections and pyelonephritis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to be necessary.

Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents (see sections 4.4 and 5.1).

4.2 Posology and method of administration

The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to ciprofloxacin of the causative organism(s), the renal function of the patient and, in children and adolescents the body weight.

The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course.

After intravenous initiation of treatment, the treatment can be switched to oral treatment with tablet or suspension if clinically indicated at the discretion of the physician. IV treatment should be followed by oral route as soon as possible.
In severe cases or if the patient is unable to take tablets (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

Treatment of infections due to certain bacteria (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* or *Staphylococci)* may require higher ciprofloxacin doses and co-administration with other appropriate antibacterial agents.

Treatment of some infections (e.g. pelvic inflammatory disease, intra-abdominal infections, infections in neutropenic patients and infections of bones and joints) may require co-administration with other appropriate antibacterial agents depending on the pathogens involved.

Adults

Indications		**Daily dose in mg**	**Total duration of treatment (including switch to oral therapy as soon as possible)**
Infections of the lower respiratory tract		400 mg twice daily to 400 mg three times a day	7 to 14 days
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	400 mg twice daily to 400 mg three times a day	7 to 14 days

Indications		**Daily dose in mg**	**Total duration of treatment (including switch to oral therapy as soon as possible)**
	Chronic suppurative otitis media	400 mg twice daily to 400 mg three times a day	7 to 14 days
	Malignant external otitis	400 mg three times a day	28 days up to 3 months
Urinary tract infections	Complicated and uncomplicated pyelonephritis	400 mg twice daily to 400 mg three times a day	7 to 21 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Prostatitis	400 mg twice daily to 400 mg three times a day	2 to 4 weeks (acute)
Genital tract infections	Epididymo-orchitis and pelvic inflammatory diseases	400 mg twice daily to 400 mg three times a day	at least 14 days
Infections of the gastro-intestinal tract and intra-abdominal infections	Diarrhoea caused by bacterial pathogens including *Shigella* spp. other than *Shigella dysenteriae* type 1 and empirical treatment of severe travellers' diarrhoea	400 mg twice daily	1 day
	Diarrhoea caused by *Shigella dysenteriae* type 1	400 mg twice daily	5 days
	Diarrhoea caused by *Vibrio cholerae*	400 mg twice daily	3 days
	Typhoid fever	400 mg twice daily	7 days
	Intra-abdominal infections due to Gram-negative bacteria	400 mg twice daily to 400 mg three times a day	5 to 14 days
Infections of the skin and soft tissue		400 mg twice daily to 400 mg three times a day	7 to 14 days
Bone and joint infections		400 mg twice daily to 400 mg three times a day	max. of 3 months
Treatment of infections or prophylaxis of infections in neutropenic patients Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance.		400 mg twice daily to 400 mg three times a day	Therapy should be continued over the entire period of neutropenia
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons requiring parenteral treatment Drug administration should begin as soon as possible after suspected or confirmed exposure.		400 mg twice daily	60 days from the confirmation of *Bacillus anthracis* exposure

Children and adolescents

Indication	Daily dose in mg	Total duration of treatment (including switch to oral therapy as soon as possible)
Cystic fibrosis	10 mg/kg body weight three times a day with a maximum of 400 mg per dose.	10 to 14 days
Complicated urinary tract infections and pyelonephritis	6 mg/kg body weight three times a day to 10 mg/kg body weight three times a day with a maximum of 400 mg per dose.	10 to 21 days
Inhalation anthrax post-exposure curative treatment for persons requiring parenteral treatment Drug administration should begin as soon as possible after suspected or confirmed exposure.	10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 400 mg per dose.	60 days from the confirmation of *Bacillus anthracis* exposure
Other severe infections	10 mg/kg body weight three times a day with a maximum of 400 mg per dose.	According to the type of infections

Geriatric patients

Geriatric patients should receive a dose selected according to the severity of the infection and the patient`s creatinine clearance.

Renal and hepatic impairment

Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance [mL/min/1.73 m²]	Serum Creatinine [µmol/L]	Intravenous Dose [mg]
> 60	< 124	See Usual Dosage.
30-60	124 to 168	200-400 mg every 12 h
< 30	> 169	200-400 mg every 24 h
Patients on haemodialysis	> 169	200-400 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	200-400 mg every 24 h

In patients with impaired liver function no dose adjustment is required.

Dosing in children with impaired renal and/or hepatic function has not been studied.

Method of administration

Ciprofloxacin Bayer should be checked visually prior to use. It must not be used if cloudy.

Ciprofloxacin should be administered by intravenous infusion. For children, the infusion duration is 60 minutes.
In adult patients, infusion time is 60 minutes for 400 mg Ciprofloxacin Bayer and 30 minutes for 200 mg Ciprofloxacin Bayer. Slow infusion into a large vein will minimise patient discomfort and reduce the risk of venous irritation.
The infusion solution can be infused either directly or after mixing with other compatible infusion solutions (see section 6.2).

4.3 Contraindications

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients (see section 6.1).

- Concomitant administration of ciprofloxacin and tizanidine (see section 4.5).

4.4 Special warnings and precautions for use

Severe infections and mixed infections with Gram-positive and anaerobic pathogens
Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections ciprofloxacin must be co-administered with other appropriate antibacterial agents.

Streptococcal Infections (including Streptococcus pneumoniae)
Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Genital tract infections
Epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*. Ciprofloxacin should be co-administered with another appropriate antibacterial agent unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Intra-abdominal infections
There are limited data on the efficacy of ciprofloxacin in the treatment of post-surgical intra-abdominal infections.

Travellers' diarrhoea
The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited.

Infections of the bones and joints
Ciprofloxacin should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation.

Inhalational anthrax
Use in humans is based on in-vitro susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and /or international consensus documents regarding the treatment of anthrax.

Children and adolescents
The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. Safety data from a randomised double-blind study on ciprofloxacin use in children (ciprofloxacin:

n=335, mean age = 6.3 years; comparators: n=349, mean age = 6.2 years; age range = 1 to 17 years) revealed an incidence of suspected drug-related arthropathy (discerned from joint-related clinical signs and symptoms) by Day +42 of 7.2% and 4.6%. Respectively, an incidence of drug-related arthropathy by 1-year follow-up was 9.0% and 5.7%. The increase of suspected drug-related arthropathy cases over time was not statistically significant between groups. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue.

Broncho-pulmonary infections in cystic fibrosis
Clinical trials have included children and adolescents aged 5-17 years. More limited experience is available in treating children between 1 and 5 years of age.

Complicated urinary tract infections and pyelonephritis
Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.
Clinical trials have included children and adolescents aged 1-17 years.

Other specific severe infections
Other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify a ciprofloxacin use.
The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with these infections.

Hypersensitivity
Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose (see section 4.8) and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.

Musculoskeletal System
Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.
Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, as soon as the first 48 hours of treatment. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids (see section 4.8).
At any sign of tendinitis (e.g. painful swelling, inflammation), ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected limb at rest.
Ciprofloxacin should be used with caution in patients with myasthenia gravis (see section 4.8).

Photosensitivity
Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking ciprofloxacin should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment (see section 4.8).

Central Nervous System
Quinolones are known to trigger seizures or lower the seizure threshold. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued (see section 4.8). Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to self-endangering behaviour. In these cases, ciprofloxacin should be discontinued.
Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving ciprofloxacin.

Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see section 4.8).

Cardiac disorders
Since ciprofloxacin is associated with cases of QT prolongation (see section 4.8), caution should be exercised when treating patients at risk for torsades de pointes arrhythmia.

Gastrointestinal System
The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment (see section 4.8). In such cases, ciprofloxacin should immediately be discontinued, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.

Renal and urinary system
Crystalluria related to the use of ciprofloxacin has been reported (see section 4.8). Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

Hepatobiliary system
Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see section 4.8). In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued.

Glucose-6-phosphate dehydrogenase deficiency
Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.

Resistance
During or following a course of treatment with ciprofloxacin bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas* species.

Cytochrome P450
Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, ropinirole, tizanidine). Co-administration of ciprofloxacin and tizanidine is contra-indicated. Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5).

Methotrexate
The concomitant use of ciprofloxacin with methotrexate is not recommended (see section 4.5).

Interaction with tests
The *in-vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients currently taking ciprofloxacin.

Injection Site Reaction
Local intravenous site reactions have been reported with the intravenous administration of ciprofloxacin. These reactions are more frequent if the infusion time is 30 minutes or less. These may appear as local skin reactions which resolve rapidly upon completion of the infusion. Subsequent intravenous administration is not contraindicated unless the reactions recur or worsen.

Glucose Load
Ciprofloxacin Bayer solution for infusion contains 5 g glucose in 100 mL solution for infusion. This should be taken into account in patients with diabetes mellitus.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on ciprofloxacin:

Probenecid

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.

Effects of ciprofloxacin on other medicinal products:

Tizanidine

Tizanidine must not be administered together with ciprofloxacin (see section 4.3). In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

Theophylline

Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary (see section 4.4).

Other xanthine derivatives

On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivatives were reported.

Phenytoin

Simultaneous administration of ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin such that monitoring of drug levels is recommended.

Oral anticoagulants

Simultaneous administration of ciprofloxacin with warfarin may augment its anti-coagulant effects. There have been many reports of increases in oral anti-coagulant activity in patients receiving antibacterial agents, including fluoroquinolones. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the fluoroquinolone to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anticoagulant agent.

Ropinirole

It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, results in an increase of C_{max} and AUC of ropinirole by 60% and 84%, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin (see section 4.4).

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy
The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism / foetus (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

Lactation
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are nausea, diarrhoea, vomiting, transient increase in transaminases, rash, and injection and infusion site reactions.

ADRs derived from clinical studies and post-marketing surveillance with Ciprofloxacin Bayer (oral, intravenous and sequential therapy) sorted by categories of frequency are listed below. The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin.

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Infections and Infestations		Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4)		

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (life-threatening) (see section 4.4) Serum sickness-like reaction	
Metabolism and Nutrition Disorders		Anorexia	Hyperglycaemia		
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression Hallucinations	Psychotic reactions (see section 4.4)	
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (see section 4.4) Vertigo	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension	Peripheral neuropathy (see section 4.4)
Eye Disorders			Visual disturbances	Visual colour distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss / Hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia, QT prolongation, torsades de pointes *
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Cholestatic icterus Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)	
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions (see section 4.4)	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	
Musculoskeletal, Connective Tissue and Bone Disorders		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) (see section 4.4) Exacerbation of symptoms of myasthenia gravis (see section 4.4)	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria (see section 4.4) Tubulointerstitial nephritis		

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	**Frequency not known** (cannot be estimated from available data)
General Disorders and Administration Site Conditions	Injection and infusion site reactions (only intravenous administration)	Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Prothrombin level abnormal Increased amylase		

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see section 4.4).

The following undesirable effects have a higher frequency category in the subgroups of patients receiving intravenous or sequential (intravenous to oral) treatment:

Common	Vomiting, Transient increase in transaminases, Rash
Uncommon	Thrombocytopenia, Thrombocytaemia, Confusion and disorientation, Hallucinations, Par- and dysaesthesia, Seizures, Vertigo, Visual disturbances, Hearing loss, Tachycardia, Vasodilatation, Hypotension, Transient hepatic impairment, Cholestatic icterus, Renal failure, Oedema
Rare	Pancytopenia, Bone marrow depression, Anaphylactic shock, Psychotic reactions, Migraine, Olfactory nerve disorders, Hearing impaired, Vasculitis, Pancreatitis, Liver necrosis, Petechiae, Tendon rupture

Paediatric patients

The incidence of arthropathy, mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see section 4.4).

4.9 Overdose

An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.
Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has been reported.

Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated. Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02

Mechanism of action:

As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

PK/PD relationship:

Efficacy mainly depends on the relation between the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

Mechanism of resistance:

In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.
Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All *in-vitro* mechanisms of resistance are commonly observed in clinical isolates.
Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to ciprofloxacin.
Plasmid-mediated resistance encoded by qnr-genes has been reported.

Spectrum of antibacterial activity:

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

Microorganisms	Susceptible	Resistant
Enterobacteria	S ≤ 0.5 mg/L	R > 1 mg/L
Pseudomonas	S ≤ 0.5 mg/L	R > 1 mg/L
Acinetobacter	S ≤ 1 mg/L	R > 1 mg/L
Staphylococcus spp.[1]	S ≤ 1 mg/L	R > 1 mg/L
Haemophilus influenzae and *Moraxella catarrhalis*	S ≤ 0.5 mg/L	R > 0.5 mg/L
Neisseria gonorrhoeae	S ≤ 0.03 mg/L	R > 0.06 mg/L
Neisseria meningitidis	S ≤ 0.03 mg/L	R > 0.06 mg/L
Non-species-related breakpoints*	S ≤ 0.5 mg/L	R > 1 mg/L

1 *Staphylococcus* spp. - breakpoints for ciprofloxacin relate to high dose therapy.
* Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Groupings of relevant species according to ciprofloxacin susceptibility (for Streptococcus species see section 4.4)

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms *Bacillus anthracis* (1)
Aerobic Gram-negative micro-organisms *Aeromonas* spp. *Brucella* spp. *Citrobacter koseri* *Francisella tularensis* *Haemophilus ducreyi* *Haemophilus influenzae** *Legionella* spp. *Moraxella catarrhalis** *Neisseria meningitidis* *Pasteurella* spp. *Salmonella* spp.* *Shigella* spp. * *Vibrio* spp. *Yersinia pestis*
Anaerobic micro-organisms *Mobiluncus*
Other micro-organisms *Chlamydia trachomatis* ($) *Chlamydia pneumoniae* ($) *Mycoplasma hominis* ($) *Mycoplasma pneumoniae* ($)
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* ($) *Staphylococcus* spp. *(2)
Aerobic Gram-negative micro-organisms *Acinetobacter baumannii*$^{+}$ *Burkholderia cepacia* $^{+}$* *Campylobacter* spp.$^{+}$* *Citrobacter freundii** *Enterobacter aerogenes* *Enterobacter cloacae ** *Escherichia coli** *Klebsiella oxytoca* *Klebsiella pneumoniae** *Morganella morganii** *Neisseria gonorrhoeae** *Proteus mirabilis** *Proteus vulgaris** *Providencia* spp. *Pseudomonas aeruginosa** *Pseudomonas fluorescens* *Serratia marcescens**
Anaerobic micro-organisms *Peptostreptococcus* spp. *Propionibacterium acnes*

INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms *Actinomyces* *Enteroccus faecium* *Listeria monocytogenes*
Aerobic Gram-negative micro-organisms *Stenotrophomonas maltophilia*
Anaerobic micro-organisms Excepted as listed above
Other micro-organisms *Mycoplasma genitalium* *Ureaplasma urealitycum*
* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications + Resistance rate ≥ 50% in one or more EU countries ($): Natural intermediate susceptibility in the absence of acquired mechanism of resistance (1): Studies have been conducted in experimental animal infections due to inhalations of *Bacillus anthracis* spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on *in-vitro* susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and /or international consensus documents regarding treatment of anthrax. (2): Methicillin-resistant *S. aureus* very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.

5.2 Pharmacokinetic properties

Absorption

Following an intravenous infusion of ciprofloxacin the mean maximum serum concentrations were achieved at the end of infusion. Pharmacokinetics of ciprofloxacin were linear over the dose range up to 400 mg administered intravenously.

Comparison of the pharmacokinetic parameters for a twice a day and three times a day intravenous dose regimen indicated no evidence of drug accumulation for ciprofloxacin and its metabolites.

A 60-minute intravenous infusion of 200 mg ciprofloxacin or the oral administration of 250 mg ciprofloxacin, both given every 12 hours, produced an equivalent area under the serum concentration time curve (AUC).

A 60-minute intravenous infusion of 400 mg ciprofloxacin every 12 hours was bioequivalent to a 500 mg oral dose every 12 hours with regard to AUC.

The 400 mg intravenous dose administered over 60 minutes every 12 hours resulted in a C_{max} similar to that observed with a 750 mg oral dose.

A 60-minute infusion of 400 mg ciprofloxacin every 8 hours is equivalent with respect to AUC to 750 mg oral regimen given every 12 hours.

Distribution

Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin

reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Metabolism

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). The metabolites display *in-vitro* antimicrobial activity but to a lower degree than the parent compound.

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally.

Excretion of ciprofloxacin (% of dose)		
	Intravenous Administration	
	Urine	**Faeces**
Ciprofloxacin	61.5	15.2
Metabolites (M_1-M_4)	9.5	2.6

Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half lives of ciprofloxacin of up to 12 h.

Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Paediatric patients

The pharmacokinetic data in paediatric patients are limited.

In a study in children C_{max} and AUC were not age-dependent (above one year of age). No notable increase in C_{max} and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C_{max} was 6.1 mg/L (range 4.6-8.3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.7-11.8 mg/L) for children between 1 and 5 years of age. The AUC values were 17.4 mg*h/L (range 11.8-32.0 mg*h/L) and 16.5 mg*h/L (range 11.0-23.8 mg*h/L) in the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4-5 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction.
Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/ photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin *in-vitro* and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability:
As reported for other gyrase inhibitors, ciprofloxacin causes damage to the large weight-bearing joints in immature animals. The extent of the cartilage damage varies according to age, species and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs, ciprofloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal and other handling

Since the infusion solution is photosensitive, the infusion bags should be removed from the box only immediately before use. In daylight conditions complete efficacy is guaranteed for a period of three days.

Any unused solution should be disposed off.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally.]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally.]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 400 mg/200 mL solution for infusion
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ciprofloxacin Bayer 400 mg/200 mL solution for infusion is indicated for the treatment of the following infections (see sections 4.4 and 5.1). Special attention should be paid to available information on resistance to ciprofloxacin before commencing therapy.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Adults

- Lower respiratory tract infections due to Gram-negative bacteria
  - exacerbations of chronic obstructive pulmonary disease
  - broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
  - pneumonia
- Chronic suppurative otitis media
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
- Urinary tract infections
- Epididymo-orchitis including cases due to *Neisseria gonorrhoeae*
- Pelvic inflammatory disease including cases due to *Neisseria gonorrhoeae*

In the above genital tract infections when thought or known to be due to *Neisseria gonorrhoeae* it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility based on laboratory testing.

- Infections of the gastro-intestinal tract (e.g. travellers` diarrhoea)
- Intra-abdominal infections
- Infections of the skin and soft tissue caused by Gram-negative bacteria
- Malignant external otitis

- Infections of the bones and joints
- Treatment of infections in neutropenic patients
- Prophylaxis of infections in neutropenic patients
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Children and adolescents

- Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*
- Complicated urinary tract infections and pyelonephritis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to be necessary.

Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents (see sections 4.4 and 5.1).

4.2 Posology and method of administration

The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to ciprofloxacin of the causative organism(s), the renal function of the patient and, in children and adolescents the body weight.

The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course.

After intravenous initiation of treatment, the treatment can be switched to oral treatment with tablet or suspension if clinically indicated at the discretion of the physician. IV treatment should be followed by oral route as soon as possible.
In severe cases or if the patient is unable to take tablets (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

Treatment of infections due to certain bacteria (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* or *Staphylococci)* may require higher ciprofloxacin doses and co-administration with other appropriate antibacterial agents.

Treatment of some infections (e.g. pelvic inflammatory disease, intra-abdominal infections, infections in neutropenic patients and infections of bones and joints) may require co-administration with other appropriate antibacterial agents depending on the pathogens involved.

Adults

Indications		**Daily dose in mg**	**Total duration of treatment (including switch to oral therapy as soon as possible)**
Infections of the lower respiratory tract		400 mg twice daily to 400 mg three times a day	7 to 14 days
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	400 mg twice daily to 400 mg three times a day	7 to 14 days

Indications		**Daily dose in mg**	**Total duration of treatment (including switch to oral therapy as soon as possible)**
	Chronic suppurative otitis media	400 mg twice daily to 400 mg three times a day	7 to 14 days
	Malignant external otitis	400 mg three times a day	28 days up to 3 months
Urinary tract infections	Complicated and uncomplicated pyelonephritis	400 mg twice daily to 400 mg three times a day	7 to 21 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Prostatitis	400 mg twice daily to 400 mg three times a day	2 to 4 weeks (acute)
Genital tract infections	Epididymo-orchitis and pelvic inflammatory diseases	400 mg twice daily to 400 mg three times a day	at least 14 days
Infections of the gastro-intestinal tract and intra-abdominal infections	Diarrhoea caused by bacterial pathogens including *Shigella* spp. other than *Shigella dysenteriae* type 1 and empirical treatment of severe travellers' diarrhoea	400 mg twice daily	1 day
	Diarrhoea caused by *Shigella dysenteriae* type 1	400 mg twice daily	5 days
	Diarrhoea caused by *Vibrio cholerae*	400 mg twice daily	3 days
	Typhoid fever	400 mg twice daily	7 days
	Intra-abdominal infections due to Gram-negative bacteria	400 mg twice daily to 400 mg three times a day	5 to 14 days
Infections of the skin and soft tissue		400 mg twice daily to 400 mg three times a day	7 to 14 days
Bone and joint infections		400 mg twice daily to 400 mg three times a day	max. of 3 months
Treatment of infections or prophylaxis of infections in neutropenic patients Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance.		400 mg twice daily to 400 mg three times a day	Therapy should be continued over the entire period of neutropenia
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons requiring parenteral treatment Drug administration should begin as soon as possible after suspected or confirmed exposure.		400 mg twice daily	60 days from the confirmation of *Bacillus anthracis* exposure

Children and adolescents

Indication	**Daily dose in mg**	**Total duration of treatment (including switch to oral therapy as soon as possible)**
Cystic fibrosis	10 mg/kg body weight three times a day with a maximum of 400 mg per dose.	10 to 14 days
Complicated urinary tract infections and pyelonephritis	6 mg/kg body weight three times a day to 10 mg/kg body weight three times a day with a maximum of 400 mg per dose.	10 to 21 days
Inhalation anthrax post-exposure curative treatment for persons requiring parenteral treatment Drug administration should begin as soon as possible after suspected or confirmed exposure.	10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 400 mg per dose.	60 days from the confirmation of *Bacillus anthracis* exposure
Other severe infections	10 mg/kg body weight three times a day with a maximum of 400 mg per dose.	According to the type of infections

Geriatric patients

Geriatric patients should receive a dose selected according to the severity of the infection and the patient`s creatinine clearance.

Renal and hepatic impairment

Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance [mL/min/1.73 m²]	**Serum Creatinine [µmol/L]**	**Intravenous Dose [mg]**
> 60	< 124	See Usual Dosage.
30-60	124 to 168	200-400 mg every 12 h
< 30	> 169	200-400 mg every 24 h
Patients on haemodialysis	> 169	200-400 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	200-400 mg every 24 h

In patients with impaired liver function no dose adjustment is required.

Dosing in children with impaired renal and/or hepatic function has not been studied.

Method of administration

Ciprofloxacin Bayer should be checked visually prior to use. It must not be used if cloudy.

Ciprofloxacin should be administered by intravenous infusion. For children, the infusion duration is 60 minutes.
In adult patients, infusion time is 60 minutes for 400 mg Ciprofloxacin Bayer and 30 minutes for 200 mg Ciprofloxacin Bayer. Slow infusion into a large vein will minimise patient discomfort and reduce the risk of venous irritation.
The infusion solution can be infused either directly or after mixing with other compatible infusion solutions (see section 6.2).

4.3 Contraindications

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients (see section 6.1).

- Concomitant administration of ciprofloxacin and tizanidine (see section 4.5).

4.4 Special warnings and precautions for use

Severe infections and mixed infections with Gram-positive and anaerobic pathogens
Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections ciprofloxacin must be co-administered with other appropriate antibacterial agents.

Streptococcal Infections (including Streptococcus pneumoniae)
Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Genital tract infections
Epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*. Ciprofloxacin should be co-administered with another appropriate antibacterial agent unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Intra-abdominal infections
There are limited data on the efficacy of ciprofloxacin in the treatment of post-surgical intra-abdominal infections.

Travellers' diarrhoea
The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited.

Infections of the bones and joints
Ciprofloxacin should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation.

Inhalational anthrax
Use in humans is based on in-vitro susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and /or international consensus documents regarding the treatment of anthrax.

Children and adolescents
The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. Safety data from a randomised double-blind study on ciprofloxacin use in children (ciprofloxacin: n=335, mean age = 6.3 years; comparators: n=349, mean age = 6.2 years; age range = 1 to 17 years) revealed an incidence of suspected drug-related arthropathy (discerned from joint-related clinical signs and symptoms) by Day +42 of 7.2% and 4.6%. Respectively, an incidence of drug-related arthropathy by 1-year follow-up was 9.0% and 5.7%. The increase of suspected drug-related arthropathy cases over time was not statistically significant between groups. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue.

Broncho-pulmonary infections in cystic fibrosis
Clinical trials have included children and adolescents aged 5-17 years. More limited experience is available in treating children between 1 and 5 years of age.

Complicated urinary tract infections and pyelonephritis
Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.
Clinical trials have included children and adolescents aged 1-17 years.

Other specific severe infections
Other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify a ciprofloxacin use.
The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with these infections.

Hypersensitivity
Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose (see section 4.8) and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.

Musculoskeletal System
Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.
Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, as soon as the first 48 hours of treatment. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids (see section 4.8).
At any sign of tendinitis (e.g. painful swelling, inflammation), ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected limb at rest.
Ciprofloxacin should be used with caution in patients with myasthenia gravis (see section 4.8).

Photosensitivity
Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking ciprofloxacin should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment (see section 4.8).

Central Nervous System
Quinolones are known to trigger seizures or lower the seizure threshold. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur Ciprofloxacin should be discontinued (see section 4.8). Psychiatric reactions may occur even after the

first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to self-endangering behaviour. In these cases, ciprofloxacin should be discontinued.
Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving ciprofloxacin. Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see section 4.8).

Cardiac disorders
Since ciprofloxacin is associated with cases of QT prolongation (see section 4.8), caution should be exercised when treating patients at risk for torsades de pointes arrhythmia.

Gastrointestinal System
The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment (see section 4.8). In such cases, ciprofloxacin should immediately be discontinued, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.

Renal and urinary system
Crystalluria related to the use of ciprofloxacin has been reported (see section 4.8). Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

Hepatobiliary system
Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see section 4.8). In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued.

Glucose-6-phosphate dehydrogenase deficiency
Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.

Resistance
During or following a course of treatment with ciprofloxacin bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas* species.

Cytochrome P450
Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, ropinirole, tizanidine). Co-administration of ciprofloxacin and tizanidine is contra-indicated. Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5).

Methotrexate
The concomitant use of ciprofloxacin with methotrexate is not recommended (see section 4.5).

Interaction with tests
The *in-vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients currently taking ciprofloxacin.

Injection Site Reaction
Local intravenous site reactions have been reported with the intravenous administration of ciprofloxacin. These reactions are more frequent if the infusion time is 30 minutes or less. These may appear as local skin reactions which resolve rapidly upon completion of the infusion. Subsequent intravenous administration is not contraindicated unless the reactions recur or worsen.

Glucose Load
Ciprofloxacin Bayer solution for infusion contains 10 g glucose in 200 mL solution for infusion. This should be taken into account in patients with diabetes mellitus.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on ciprofloxacin:

Probenecid

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.

Effects of ciprofloxacin on other medicinal products:

Tizanidine

Tizanidine must not be administered together with ciprofloxacin (see section 4.3). In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

Theophylline

Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary (see section 4.4).

Other xanthine derivatives

On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivatives were reported.

Phenytoin

Simultaneous administration of ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin such that monitoring of drug levels is recommended.

Oral anticoagulants

Simultaneous administration of ciprofloxacin with warfarin may augment its anti-coagulant effects. There have been many reports of increases in oral anti-coagulant activity in patients receiving antibacterial agents, including fluoroquinolones. The risk may vary with the underlying infection, age

and general status of the patient so that the contribution of the fluoroquinolone to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anticoagulant agent.

Ropinirole

It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, results in an increase of C_{max} and AUC of ropinirole by 60% and 84%, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin (see section 4.4).

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy
The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism / foetus (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

Lactation
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are nausea, diarrhoea, vomiting, transient increase in transaminases, rash, and injection and infusion site reactions.

ADRs derived from clinical studies and post-marketing surveillance with Ciprofloxacin Bayer (oral, intravenous and sequential therapy) sorted by categories of frequency are listed below. The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin.

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Infections and Infestations		Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4)		
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (life-threatening) (see section 4.4) Serum sickness-like reaction	
Metabolism and Nutrition Disorders		Anorexia	Hyperglycaemia		
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression Hallucinations	Psychotic reactions (see section 4.4)	
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (see section 4.4) Vertigo	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension	Peripheral neuropathy (see section 4.4)
Eye Disorders			Visual disturbances	Visual colour distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss / Hearing impaired		

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Cardiac Disorders			Tachycardia		Ventricular arrhythmia, QT prolongation, torsades de pointes *
Vascular Disorders			Vasodilation Hypotension Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Cholestatic icterus Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)	
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions (see section 4.4)	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Musculoskeletal, Connective Tissue and Bone Disorders		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) (see section 4.4) Exacerbation of symptoms of myasthenia gravis (see section 4.4)	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria (see section 4.4) Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions	Injection and infusion site reactions (only intravenous administration)	Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Prothrombin level abnormal Increased amylase		

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see section 4.4).

The following undesirable effects have a higher frequency category in the subgroups of patients receiving intravenous or sequential (intravenous to oral) treatment:

Common	Vomiting, Transient increase in transaminases, Rash
Uncommon	Thrombocytopenia, Thrombocytaemia, Confusion and disorientation, Hallucinations, Par- and dysaesthesia, Seizures, Vertigo, Visual disturbances, Hearing loss, Tachycardia, Vasodilatation, Hypotension, Transient hepatic impairment, Cholestatic icterus, Renal failure, Oedema
Rare	Pancytopenia, Bone marrow depression, Anaphylactic shock, Psychotic reactions, Migraine, Olfactory nerve disorders, Hearing impaired, Vasculitis, Pancreatitis, Liver necrosis, Petechiae, Tendon rupture

Paediatric patients

The incidence of arthropathy, mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see section 4.4).

4.9 Overdose

An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.
Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has been reported.

Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated. Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02

Mechanism of action:

As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

PK/PD relationship:

Efficacy mainly depends on the relation between the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

Mechanism of resistance:

In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.
Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All *in-vitro* mechanisms of resistance are commonly observed in clinical isolates.
Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to ciprofloxacin.
Plasmid-mediated resistance encoded by qnr-genes has been reported.

Spectrum of antibacterial activity:

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

Microorganisms	Susceptible	Resistant
Enterobacteria	S ≤ 0.5 mg/L	R > 1 mg/L
Pseudomonas	S ≤ 0.5 mg/L	R > 1 mg/L
Acinetobacter	S ≤ 1 mg/L	R > 1 mg/L
Staphylococcus spp.[1]	S ≤ 1 mg/L	R > 1 mg/L

Haemophilus influenzae and *Moraxella catarrhalis*	S ≤ 0.5 mg/L	R > 0.5 mg/L
Neisseria gonorrhoeae	S ≤ 0.03 mg/L	R > 0.06 mg/L
Neisseria meningitidis	S ≤ 0.03 mg/L	R > 0.06 mg/L
Non-species-related breakpoints*****	S ≤ 0.5 mg/L	R > 1 mg/L

1 *Staphylococcus* spp. - breakpoints for ciprofloxacin relate to high dose therapy.

* Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Groupings of relevant species according to ciprofloxacin susceptibility (for Streptococcus species see section 4.4)

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms *Bacillus anthracis* (1)
Aerobic Gram-negative micro-organisms *Aeromonas* spp. *Brucella* spp. *Citrobacter koseri* *Francisella tularensis* *Haemophilus ducreyi* *Haemophilus influenzae** *Legionella* spp. *Moraxella catarrhalis** *Neisseria meningitidis* *Pasteurella* spp. *Salmonella* spp.*** *Shigella* spp. *** *Vibrio* spp. *Yersinia pestis*
Anaerobic micro-organisms *Mobiluncus*
Other micro-organisms *Chlamydia trachomatis* ($) *Chlamydia pneumoniae* ($) *Mycoplasma hominis* ($) *Mycoplasma pneumoniae* ($)
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* ($) *Staphylococcus* spp. *(2)

Aerobic Gram-negative micro-organisms *Acinetobacter baumannii*[+] *Burkholderia cepacia* [+]* *Campylobacter* spp.[+]* *Citrobacter freundii** *Enterobacter aerogenes* *Enterobacter cloacae ** *Escherichia coli** *Klebsiella oxytoca* *Klebsiella pneumoniae** *Morganella morganii** *Neisseria gonorrhoeae** *Proteus mirabilis** *Proteus vulgaris** *Providencia* spp. *Pseudomonas aeruginosa** *Pseudomonas fluorescens* *Serratia marcescens**
Anaerobic micro-organisms *Peptostreptococcus* spp. *Propionibacterium acnes*
INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms *Actinomyces* *Enteroccus faecium* *Listeria monocytogenes*
Aerobic Gram-negative micro-organisms *Stenotrophomonas maltophilia*
Anaerobic micro-organisms Excepted as listed above
Other micro-organisms *Mycoplasma genitalium* *Ureaplasma urealitycum*
* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications [+] Resistance rate ≥ 50% in one or more EU countries ($): Natural intermediate susceptibility in the absence of acquired mechanism of resistance (1): Studies have been conducted in experimental animal infections due to inhalations of *Bacillus anthracis* spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on *in-vitro* susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and /or international consensus documents regarding treatment of anthrax. (2): Methicillin-resistant *S. aureus* very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.

5.2 Pharmacokinetic properties

Absorption

Following an intravenous infusion of ciprofloxacin the mean maximum serum concentrations were achieved at the end of infusion. Pharmacokinetics of ciprofloxacin were linear over the dose range up to 400 mg administered intravenously.

Comparison of the pharmacokinetic parameters for a twice a day and three times a day intravenous dose regimen indicated no evidence of drug accumulation for ciprofloxacin and its metabolites.

A 60-minute intravenous infusion of 200 mg ciprofloxacin or the oral administration of 250 mg ciprofloxacin, both given every 12 hours, produced an equivalent area under the serum concentration time curve (AUC).

A 60-minute intravenous infusion of 400 mg ciprofloxacin every 12 hours was bioequivalent to a 500 mg oral dose every 12 hours with regard to AUC.

The 400 mg intravenous dose administered over 60 minutes every 12 hours resulted in a C_{max} similar to that observed with a 750 mg oral dose.

A 60-minute infusion of 400 mg ciprofloxacin every 8 hours is equivalent with respect to AUC to 750 mg oral regimen given every 12 hours.

Distribution

Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Metabolism

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). The metabolites display *in-vitro* antimicrobial activity but to a lower degree than the parent compound.

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally.

Excretion of ciprofloxacin (% of dose)		
	Intravenous Administration	
	Urine	**Faeces**
Ciprofloxacin	61.5	15.2
Metabolites (M_1-M_4)	9.5	2.6

Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half lives of ciprofloxacin of up to 12 h.

Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Paediatric patients

The pharmacokinetic data in paediatric patients are limited.

In a study in children C_{max} and AUC were not age-dependent (above one year of age). No notable increase in C_{max} and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C_{max} was 6.1 mg/L (range 4.6-8.3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.7-11.8 mg/L) for children between 1 and 5 years of age. The AUC values were 17.4 mg*h/L (range 11.8-32.0 mg*h/L) and 16.5 mg*h/L (range 11.0-23.8 mg*h/L) in the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4-5 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction.
Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/ photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin *in-vitro* and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability:
As reported for other gyrase inhibitors, ciprofloxacin causes damage to the large weight-bearing joints in immature animals. The extent of the cartilage damage varies according to age, species and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs, ciprofloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal and other handling

Since the infusion solution is photosensitive, the infusion bags should be removed from the box only immediately before use. In daylight conditions complete efficacy is guaranteed for a period of three days.

Any unused solution should be disposed off.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally.]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally.]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 100 mg/50 mL solution for infusion
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ciprofloxacin Bayer 100 mg/50 mL solution for infusion is indicated for the treatment of the following infections (see sections 4.4 and 5.1). Special attention should be paid to available information on resistance to ciprofloxacin before commencing therapy.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Adults

- Lower respiratory tract infections due to Gram-negative bacteria
  - exacerbations of chronic obstructive pulmonary disease
  - broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
  - pneumonia
- Chronic suppurative otitis media
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
- Urinary tract infections
- Epididymo-orchitis including cases due to *Neisseria gonorrhoeae*
- Pelvic inflammatory disease including cases due to *Neisseria gonorrhoeae*

In the above genital tract infections when thought or known to be due to *Neisseria gonorrhoeae* it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility based on laboratory testing.

- Infections of the gastro-intestinal tract (e.g. travellers` diarrhoea)
- Intra-abdominal infections
- Infections of the skin and soft tissue caused by Gram-negative bacteria
- Malignant external otitis

- Infections of the bones and joints
- Treatment of infections in neutropenic patients
- Prophylaxis of infections in neutropenic patients
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Children and adolescents

- Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*
- Complicated urinary tract infections and pyelonephritis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to be necessary.

Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents (see sections 4.4 and 5.1).

4.2 Posology and method of administration

The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to ciprofloxacin of the causative organism(s), the renal function of the patient and, in children and adolescents the body weight.

The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course.

After intravenous initiation of treatment, the treatment can be switched to oral treatment with tablet or suspension if clinically indicated at the discretion of the physician. IV treatment should be followed by oral route as soon as possible.
In severe cases or if the patient is unable to take tablets (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

Treatment of infections due to certain bacteria (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* or *Staphylococci)* may require higher ciprofloxacin doses and co-administration with other appropriate antibacterial agents.

Treatment of some infections (e.g. pelvic inflammatory disease, intra-abdominal infections, infections in neutropenic patients and infections of bones and joints) may require co-administration with other appropriate antibacterial agents depending on the pathogens involved.

Adults

Indications	**Daily dose in mg**	**Total duration of treatment (including switch to oral therapy as soon as possible)**
Infections of the lower respiratory tract	400 mg twice daily to 400 mg three times a day	7 to 14 days

Indications		**Daily dose in mg**	**Total duration of treatment (including switch to oral therapy as soon as possible)**
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	400 mg twice daily to 400 mg three times a day	7 to 14 days
	Chronic suppurative otitis media	400 mg twice daily to 400 mg three times a day	7 to 14 days
	Malignant external otitis	400 mg three times a day	28 days up to 3 months
Urinary tract infections	Complicated and uncomplicated pyelonephritis	400 mg twice daily to 400 mg three times a day	7 to 21 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Prostatitis	400 mg twice daily to 400 mg three times a day	2 to 4 weeks (acute)
Genital tract infections	Epididymo-orchitis and pelvic inflammatory diseases	400 mg twice daily to 400 mg three times a day	at least 14 days
Infections of the gastro-intestinal tract and intra-abdominal infections	Diarrhoea caused by bacterial pathogens including *Shigella* spp. other than *Shigella dysenteriae* type 1 and empirical treatment of severe travellers' diarrhoea	400 mg twice daily	1 day
	Diarrhoea caused by *Shigella dysenteriae* type 1	400 mg twice daily	5 days
	Diarrhoea caused by *Vibrio cholerae*	400 mg twice daily	3 days
	Typhoid fever	400 mg twice daily	7 days
	Intra-abdominal infections due to Gram-negative bacteria	400 mg twice daily to 400 mg three times a day	5 to 14 days
Infections of the skin and soft tissue		400 mg twice daily to 400 mg three times a day	7 to 14 days
Bone and joint infections		400 mg twice daily to 400 mg three times a day	max. of 3 months
Treatment of infections or prophylaxis of infections in neutropenic patients Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance.		400 mg twice daily to 400 mg three times a day	Therapy should be continued over the entire period of neutropenia
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons requiring parenteral treatment Drug administration should begin as soon		400 mg twice daily	60 days from the confirmation of *Bacillus anthracis* exposure

Indications	Daily dose in mg	Total duration of treatment (including switch to oral therapy as soon as possible)
as possible after suspected or confirmed exposure.		

Children and adolescents

Indication	Daily dose in mg	Total duration of treatment (including switch to oral therapy as soon as possible)
Cystic fibrosis	10 mg/kg body weight three times a day with a maximum of 400 mg per dose.	10 to 14 days
Complicated urinary tract infections and pyelonephritis	6 mg/kg body weight three times a day to 10 mg/kg body weight three times a day with a maximum of 400 mg per dose.	10 to 21 days
Inhalation anthrax post-exposure curative treatment for persons requiring parenteral treatment Drug administration should begin as soon as possible after suspected or confirmed exposure.	10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 400 mg per dose.	60 days from the confirmation of *Bacillus anthracis* exposure
Other severe infections	10 mg/kg body weight three times a day with a maximum of 400 mg per dose.	According to the type of infections

Geriatric patients

Geriatric patients should receive a dose selected according to the severity of the infection and the patient`s creatinine clearance.

Renal and hepatic impairment

Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance [mL/min/ 1.73 m²]	Serum Creatinine [µmol/L]	Intravenous Dose [mg]
> 60	< 124	See Usual Dosage.
30-60	124 to 168	200-400 mg every 12 h
< 30	> 169	200-400 mg every 24 h
Patients on haemodialysis	> 169	200-400 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	200-400 mg every 24 h

In patients with impaired liver function no dose adjustment is required.

Dosing in children with impaired renal and/or hepatic function has not been studied.

Method of administration

Ciprofloxacin Bayer should be checked visually prior to use. It must not be used if cloudy.

Ciprofloxacin should be administered by intravenous infusion. For children, the infusion duration is 60 minutes.
In adult patients, infusion time is 60 minutes for 400 mg Ciprofloxacin Bayer and 30 minutes for 200 mg Ciprofloxacin Bayer. Slow infusion into a large vein will minimise patient discomfort and reduce the risk of venous irritation.
The infusion solution can be infused either directly or after mixing with other compatible infusion solutions (see section 6.2).

4.3 Contraindications

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients (see section 6.1).

- Concomitant administration of ciprofloxacin and tizanidine (see section 4.5).

4.4 Special warnings and precautions for use

Severe infections and mixed infections with Gram-positive and anaerobic pathogens
Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections ciprofloxacin must be co-administered with other appropriate antibacterial agents.

Streptococcal Infections (including Streptococcus pneumoniae)
Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Genital tract infections
Epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*. Ciprofloxacin should be co-administered with another appropriate antibacterial agent unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Intra-abdominal infections
There are limited data on the efficacy of ciprofloxacin in the treatment of post-surgical intra-abdominal infections.

Travellers' diarrhoea
The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited.

Infections of the bones and joints
Ciprofloxacin should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation.

Inhalational anthrax
Use in humans is based on in-vitro susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and /or international consensus documents regarding the treatment of anthrax.

Children and adolescents
The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. Safety data from a randomised double-blind study on ciprofloxacin use in children (ciprofloxacin: n=335, mean age = 6.3 years; comparators: n=349, mean age = 6.2 years; age range = 1 to 17 years) revealed an incidence of suspected drug-related arthropathy (discerned from joint-related clinical signs and symptoms) by Day +42 of 7.2% and 4.6%. Respectively, an incidence of drug-related arthropathy by 1-year follow-up was 9.0% and 5.7%. The increase of suspected drug-related arthropathy cases over time was not statistically significant between groups. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue.

Broncho-pulmonary infections in cystic fibrosis
Clinical trials have included children and adolescents aged 5-17 years. More limited experience is available in treating children between 1 and 5 years of age.

Complicated urinary tract infections and pyelonephritis
Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.
Clinical trials have included children and adolescents aged 1-17 years.

Other specific severe infections
Other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify a ciprofloxacin use.
The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with these infections.

Hypersensitivity
Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose (see section 4.8) and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.

Musculoskeletal System
Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.
Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, as soon as the first 48 hours of treatment. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids (see section 4.8).
At any sign of tendinitis (e.g. painful swelling, inflammation), ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected limb at rest.
Ciprofloxacin should be used with caution in patients with myasthenia gravis (see section 4.8).

Photosensitivity
Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking ciprofloxacin should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment (see section 4.8).

Central Nervous System
Quinolones are known to trigger seizures or lower the seizure threshold. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued (see section 4.8). Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to self-endangering behaviour. In these cases, ciprofloxacin should be discontinued.
Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving ciprofloxacin. Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see section 4.8).

Cardiac disorders
Since ciprofloxacin is associated with cases of QT prolongation (see section 4.8), caution should be exercised when treating patients at risk for torsades de pointes arrhythmia.

Gastrointestinal System
The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment (see section 4.8). In such cases, ciprofloxacin should immediately be discontinued, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.

Renal and urinary system
Crystalluria related to the use of ciprofloxacin has been reported (see section 4.8). Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

Hepatobiliary system
Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see section 4.8). In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued.

Glucose-6-phosphate dehydrogenase deficiency
Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.

Resistance
During or following a course of treatment with ciprofloxacin bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas species*.

Cytochrome P450
Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, ropinirole, tizanidine). Co-administration of ciprofloxacin and tizanidine is contra-indicated. Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5).

Methotrexate
The concomitant use of ciprofloxacin with methotrexate is not recommended (see section 4.5).

Interaction with tests
The *in-vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients currently taking ciprofloxacin.

Injection Site Reaction
Local intravenous site reactions have been reported with the intravenous administration of ciprofloxacin. These reactions are more frequent if the infusion time is 30 minutes or less. These may appear as local skin reactions which resolve rapidly upon completion of the infusion. Subsequent intravenous administration is not contraindicated unless the reactions recur or worsen.

NaCl Load
In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome, etc.), the additional sodium load should be taken into account (for sodium chloride content, see section 2).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on Ciprofloxacin:

Probenecid

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.

Effects of Ciprofloxacin on other medicinal products:

Tizanidine

Tizanidine must not be administered together with Ciprofloxacin (see section 4.3). In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with Ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

Theophylline

Concurrent administration of Ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary (see section 4.4).

Other xanthine derivatives

On concurrent administration of Ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivatives were reported.

Phenytoin

Simultaneous administration of Ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin such that monitoring of drug levels is recommended.

Oral anticoagulants

Simultaneous administration of ciprofloxacin with warfarin may augment its anti-coagulant effects. There have been many reports of increases in oral anti-coagulant activity in patients receiving antibacterial agents, including fluoroquinolones. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the fluoroquinolone to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anticoagulant agent.

Ropinirole

It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, results in an increase of C_{max} and AUC of ropinirole by 60% and 84%, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin (see section 4.4).

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy
The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism / foetus (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

Lactation
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are nausea, diarrhoea, vomiting, transient increase in transaminases, rash, and injection and infusion site reactions.

ADRs derived from clinical studies and post-marketing surveillance with Ciprofloxacin Bayer (oral, intravenous and sequential therapy) sorted by categories of frequency are listed below. The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin.

System Organ Class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1 000 to < 1/100	**Rare** ≥ 1/10 000 to < 1/1 000	**Very Rare** < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Infections and Infestations		Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4)		
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (life-threatening) (see section 4.4) Serum sickness-like reaction	
Metabolism and Nutrition Disorders		Anorexia	Hyperglycaemia		
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression Hallucinations	Psychotic reactions (see section 4.4)	
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (see section 4.4) Vertigo	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension	Peripheral neuropathy (see section 4.4)

System Organ Class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1 000 to < 1/100	**Rare** ≥ 1/10 000 to < 1/1 000	**Very Rare** < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Eye Disorders			Visual disturbances	Visual colour distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss / Hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia, QT prolongation, torsades de pointes *
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Cholestatic icterus Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)	

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	Frequency not known (cannot be estimated from available data)
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions (see section 4.4)	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	
Musculoskeletal, Connective Tissue and Bone Disorders		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) (see section 4.4) Exacerbation of symptoms of myasthenia gravis (see section 4.4)	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria (see section 4.4) Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions	Injection and infusion site reactions (only intravenous administration)	Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Prothrombin level abnormal Increased amylase		

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see section 4.4).

The following undesirable effects have a higher frequency category in the subgroups of patients receiving intravenous or sequential (intravenous to oral) treatment:

Common	Vomiting, Transient increase in transaminases, Rash
Uncommon	Thrombocytopenia, Thrombocytaemia, Confusion and disorientation, Hallucinations, Par- and dysaesthesia, Seizures, Vertigo, Visual disturbances, Hearing loss, Tachycardia, Vasodilatation, Hypotension, Transient hepatic impairment, Cholestatic icterus, Renal failure, Oedema
Rare	Pancytopenia, Bone marrow depression, Anaphylactic shock, Psychotic reactions, Migraine, Olfactory nerve disorders, Hearing impaired, Vasculitis, Pancreatitis, Liver necrosis, Petechiae, Tendon rupture

Paediatric patients
The incidence of arthropathy, mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see section 4.4).

4.9 Overdose

An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.
Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has been reported.

Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated. Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02

Mechanism of action:

As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

PK/PD relationship:

Efficacy mainly depends on the relation between the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

Mechanism of resistance:

In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.

Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All *in-vitro* mechanisms of resistance are commonly observed in clinical isolates. Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to ciprofloxacin. Plasmid-mediated resistance encoded by qnr-genes has been reported.

Spectrum of antibacterial activity:

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

Microorganisms	Susceptible	Resistant
Enterobacteria	S ≤ 0.5 mg/L	R > 1 mg/L
Pseudomonas	S ≤ 0.5 mg/L	R > 1 mg/L
Acinetobacter	S ≤ 1 mg/L	R > 1 mg/L
Staphylococcus spp.[1]	S ≤ 1 mg/L	R > 1 mg/L
Haemophilus influenzae and *Moraxella catarrhalis*	S ≤ 0.5 mg/L	R > 0.5 mg/L
Neisseria gonorrhoeae	S ≤ 0.03 mg/L	R > 0.06 mg/L
Neisseria meningitidis	S ≤ 0.03 mg/L	R > 0.06 mg/L
Non-species-related breakpoints*****	S ≤ 0.5 mg/L	R > 1 mg/L

1 *Staphylococcus* spp. – breakpoints for ciprofloxacin relate to high dose therapy.

* Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Groupings of relevant species according to ciprofloxacin susceptibility (for *Streptococcus* species see section 4.4)

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms *Bacillus anthracis* (1)
Aerobic Gram-negative micro-organisms *Aeromonas* spp. *Brucella* spp. *Citrobacter koseri* *Francisella tularensis* *Haemophilus ducreyi* *Haemophilus influenzae** *Legionella* spp. *Moraxella catarrhalis** *Neisseria meningitidis* *Pasteurella* spp. *Salmonella* spp.* *Shigella* spp. * *Vibrio* spp.

Yersinia pestis
Anaerobic micro-organisms *Mobiluncus*
Other micro-organisms *Chlamydia trachomatis* ($) *Chlamydia pneumoniae* ($) *Mycoplasma hominis* ($) *Mycoplasma pneumoniae* ($)
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* ($) *Staphylococcus* spp. *(2)
Aerobic Gram-negative micro-organisms *Acinetobacter baumannii*[+] *Burkholderia cepacia* [+]* *Campylobacter* spp.[+]* *Citrobacter freundii** *Enterobacter aerogenes* *Enterobacter cloacae ** *Escherichia coli** *Klebsiella oxytoca* *Klebsiella pneumoniae** *Morganella morganii** *Neisseria gonorrhoeae** *Proteus mirabilis** *Proteus vulgaris** *Providencia* spp. *Pseudomonas aeruginosa** *Pseudomonas fluorescens* *Serratia marcescens**
Anaerobic micro-organisms *Peptostreptococcus* spp. *Propionibacterium acnes*
INHERENTLY RESISTANT ORGANISMS

Aerobic Gram-positive micro-organisms *Actinomyces* *Enteroccus faecium* *Listeria monocytogenes*
Aerobic Gram-negative micro-organisms *Stenotrophomonas maltophilia*
Anaerobic micro-organisms Excepted as listed above
Other micro-organisms *Mycoplasma genitalium* *Ureaplasma urealitycum*
* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications + Resistance rate ≥ 50% in one or more EU countries ($): Natural intermediate susceptibility in the absence of acquired mechanism of resistance (1): Studies have been conducted in experimental animal infections due to inhalations of *Bacillus anthracis* spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on *in-vitro* susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and /or international consensus documents regarding treatment of anthrax. (2): Methicillin-resistant *S. aureus* very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.

5.2 Pharmacokinetic properties

Absorption

Following an intravenous infusion of ciprofloxacin the mean maximum serum concentrations were achieved at the end of infusion. Pharmacokinetics of ciprofloxacin were linear over the dose range up to 400 mg administered intravenously.

Comparison of the pharmacokinetic parameters for a twice a day and three times a day intravenous dose regimen indicated no evidence of drug accumulation for ciprofloxacin and its metabolites.

A 60-minute intravenous infusion of 200 mg ciprofloxacin or the oral administration of 250 mg ciprofloxacin, both given every 12 hours, produced an equivalent area under the serum concentration time curve (AUC).

A 60-minute intravenous infusion of 400 mg ciprofloxacin every 12 hours was bioequivalent to a 500 mg oral dose every 12 hours with regard to AUC.

The 400 mg intravenous dose administered over 60 minutes every 12 hours resulted in a C_{max} similar to that observed with a 750 mg oral dose.

A 60-minute infusion of 400 mg ciprofloxacin every 8 hours is equivalent with respect to AUC to 750 mg oral regimen given every 12 hours.

Distribution

Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages,

biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Metabolism

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). The metabolites display *in-vitro* antimicrobial activity but to a lower degree than the parent compound.

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally.–

Excretion of ciprofloxacin (% of dose)		
	Intravenous Administration	
	Urine	**Faeces**
Ciprofloxacin	61.5	15.2
Metabolites (M_1-M_4)	9.5	2.6

Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half lives of ciprofloxacin of up to 12 h.

Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Paediatric patients

The pharmacokinetic data in paediatric patients are limited.

In a study in children C_{max} and AUC were not age-dependent (above one year of age). No notable increase in C_{max} and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C_{max} was 6.1 mg/L (range 4.6-8.3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.7-11.8 mg/L) for children between 1 and 5 years of age. The AUC values were 17.4 mg*h/L (range 11.8-32.0 mg*h/L) and 16.5 mg*h/L (range 11.0-23.8 mg*h/L) in the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4-5 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction.
Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/ photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin *in-vitro* and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability:
As reported for other gyrase inhibitors, ciprofloxacin causes damage to the large weight-bearing joints in immature animals. The extent of the cartilage damage varies according to age, species and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs, ciprofloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal and other handling

For ease of use the infusion vial stopper should be penetrated in the central ring. Penetration of the outer ring may result in damage to the vial stopper.

Any unused solution should be disposed off.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally.]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally.]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 200 mg/100 mL solution for infusion
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ciprofloxacin Bayer 200 mg/100 mL solution for infusion is indicated for the treatment of the following infections (see sections 4.4 and 5.1). Special attention should be paid to available information on resistance to ciprofloxacin before commencing therapy.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Adults

- Lower respiratory tract infections due to Gram-negative bacteria
  - exacerbations of chronic obstructive pulmonary disease
  - broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
  - pneumonia
- Chronic suppurative otitis media
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
- Urinary tract infections
- Epididymo-orchitis including cases due to *Neisseria gonorrhoeae*
- Pelvic inflammatory disease including cases due to *Neisseria gonorrhoeae*

In the above genital tract infections when thought or known to be due to *Neisseria gonorrhoeae* it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility based on laboratory testing.

- Infections of the gastro-intestinal tract (e.g. travellers` diarrhoea)
- Intra-abdominal infections
- Infections of the skin and soft tissue caused by Gram-negative bacteria
- Malignant external otitis

- Infections of the bones and joints
- Treatment of infections in neutropenic patients
- Prophylaxis of infections in neutropenic patients
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Children and adolescents

- Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*
- Complicated urinary tract infections and pyelonephritis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to be necessary.

Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents (see sections 4.4 and 5.1).

4.2 Posology and method of administration

The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to ciprofloxacin of the causative organism(s), the renal function of the patient and, in children and adolescents the body weight.

The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course.

After intravenous initiation of treatment, the treatment can be switched to oral treatment with tablet or suspension if clinically indicated at the discretion of the physician. IV treatment should be followed by oral route as soon as possible.
In severe cases or if the patient is unable to take tablets (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

Treatment of infections due to certain bacteria (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* or *Staphylococci*) may require higher ciprofloxacin doses and co-administration with other appropriate antibacterial agents.

Treatment of some infections (e.g. pelvic inflammatory disease, intra-abdominal infections, infections in neutropenic patients and infections of bones and joints) may require co-administration with other appropriate antibacterial agents depending on the pathogens involved.

Adults

Indications		**Daily dose in mg**	**Total duration of treatment (including switch to oral therapy as soon as possible)**
Infections of the lower respiratory tract		400 mg twice daily to 400 mg three times a day	7 to 14 days
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	400 mg twice daily to 400 mg three times a day	7 to 14 days

Indications		**Daily dose in mg**	**Total duration of treatment (including switch to oral therapy as soon as possible)**
	Chronic suppurative otitis media	400 mg twice daily to 400 mg three times a day	7 to 14 days
	Malignant external otitis	400 mg three times a day	28 days up to 3 months
Urinary tract infections	Complicated and uncomplicated pyelonephritis	400 mg twice daily to 400 mg three times a day	7 to 21 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Prostatitis	400 mg twice daily to 400 mg three times a day	2 to 4 weeks (acute)
Genital tract infections	Epididymo-orchitis and pelvic inflammatory diseases	400 mg twice daily to 400 mg three times a day	at least 14 days
Infections of the gastro-intestinal tract and intra-abdominal infections	Diarrhoea caused by bacterial pathogens including *Shigella* spp. other than *Shigella dysenteriae* type 1 and empirical treatment of severe travellers' diarrhoea	400 mg twice daily	1 day
	Diarrhoea caused by *Shigella dysenteriae* type 1	400 mg twice daily	5 days
	Diarrhoea caused by *Vibrio cholerae*	400 mg twice daily	3 days
	Typhoid fever	400 mg twice daily	7 days
	Intra-abdominal infections due to Gram-negative bacteria	400 mg twice daily to 400 mg three times a day	5 to 14 days
Infections of the skin and soft tissue		400 mg twice daily to 400 mg three times a day	7 to 14 days
Bone and joint infections		400 mg twice daily to 400 mg three times a day	max. of 3 months
Treatment of infections or prophylaxis of infections in neutropenic patients Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance.		400 mg twice daily to 400 mg three times a day	Therapy should be continued over the entire period of neutropenia
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons requiring parenteral treatment Drug administration should begin as soon as possible after suspected or confirmed exposure.		400 mg twice daily	60 days from the confirmation of *Bacillus anthracis* exposure

Children and adolescents

Indication	Daily dose in mg	Total duration of treatment (including switch to oral therapy as soon as possible)
Cystic fibrosis	10 mg/kg body weight three times a day with a maximum of 400 mg per dose.	10 to 14 days
Complicated urinary tract infections and pyelonephritis	6 mg/kg body weight three times a day to 10 mg/kg body weight three times a day with a maximum of 400 mg per dose.	10 to 21 days
Inhalation anthrax post-exposure curative treatment for persons requiring parenteral treatment Drug administration should begin as soon as possible after suspected or confirmed exposure.	10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 400 mg per dose.	60 days from the confirmation of *Bacillus anthracis* exposure
Other severe infections	10 mg/kg body weight three times a day with a maximum of 400 mg per dose.	According to the type of infections

Geriatric patients

Geriatric patients should receive a dose selected according to the severity of the infection and the patient`s creatinine clearance.

Renal and hepatic impairment

Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance [mL/min/1.73 m²]	Serum Creatinine [µmol/L]	Intravenous Dose [mg]
> 60	< 124	See Usual Dosage.
30-60	124 to 168	200-400 mg every 12 h
< 30	> 169	200-400 mg every 24 h
Patients on haemodialysis	> 169	200-400 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	200-400 mg every 24 h

In patients with impaired liver function no dose adjustment is required.

Dosing in children with impaired renal and/or hepatic function has not been studied.

Method of administration

Ciprofloxacin Bayer should be checked visually prior to use. It must not be used if cloudy.

Ciprofloxacin should be administered by intravenous infusion. For children, the infusion duration is 60 minutes.
In adult patients, infusion time is 60 minutes for 400 mg Ciprofloxacin Bayer and 30 minutes for 200 mg Ciprofloxacin Bayer. Slow infusion into a large vein will minimise patient discomfort and reduce the risk of venous irritation.
The infusion solution can be infused either directly or after mixing with other compatible infusion solutions (see section 6.2).

4.3 Contraindications

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients (see section 6.1).

- Concomitant administration of ciprofloxacin and tizanidine (see section 4.5).

4.4 Special warnings and precautions for use

Severe infections and mixed infections with Gram-positive and anaerobic pathogens
Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections ciprofloxacin must be co-administered with other appropriate antibacterial agents.

Streptococcal Infections (including Streptococcus pneumoniae)
Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Genital tract infections
Epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*. Ciprofloxacin should be co-administered with another appropriate antibacterial agent unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Intra-abdominal infections
There are limited data on the efficacy of ciprofloxacin in the treatment of post-surgical intra-abdominal infections.

Travellers' diarrhoea
The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited.

Infections of the bones and joints
Ciprofloxacin should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation.

Inhalational anthrax
Use in humans is based on *in-vitro* susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and /or international consensus documents regarding the treatment of anthrax.

Children and adolescents
The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. Safety data from a randomised double-blind study on ciprofloxacin use in children (ciprofloxacin: n=335, mean age = 6.3 years; comparators: n=349, mean age = 6.2 years; age range = 1 to 17 years)

revealed an incidence of suspected drug-related arthropathy (discerned from joint-related clinical signs and symptoms) by Day +42 of 7.2% and 4.6%. Respectively, an incidence of drug-related arthropathy by 1-year follow-up was 9.0% and 5.7%. The increase of suspected drug-related arthropathy cases over time was not statistically significant between groups. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue.

Broncho-pulmonary infections in cystic fibrosis
Clinical trials have included children and adolescents aged 5-17 years. More limited experience is available in treating children between 1 and 5 years of age.

Complicated urinary tract infections and pyelonephritis
Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.
Clinical trials have included children and adolescents aged 1-17 years.

Other specific severe infections
Other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify a ciprofloxacin use.
The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with these infections.

Hypersensitivity
Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose (see section 4.8) and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.

Musculoskeletal System
Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.
Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, as soon as the first 48 hours of treatment. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids (see section 4.8).
At any sign of tendinitis (e.g. painful swelling, inflammation), ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected limb at rest.
Ciprofloxacin should be used with caution in patients with myasthenia gravis (see section 4.8).

Photosensitivity
Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking ciprofloxacin should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment (see section 4.8).

Central Nervous System
Quinolones are known to trigger seizures or lower the seizure threshold. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued (see section 4.8). Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to self-endangering behaviour. In these cases, ciprofloxacin should be discontinued.
Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving ciprofloxacin. Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy, including

pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see section 4.8).

Cardiac disorders
Since ciprofloxacin is associated with cases of QT prolongation (see section 4.8), caution should be exercised when treating patients at risk for torsades de pointes arrhythmia.

Gastrointestinal System
The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment (see section 4.8). In such cases, ciprofloxacin should immediately be discontinued, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.

Renal and urinary system
Crystalluria related to the use of ciprofloxacin has been reported (see section 4.8). Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

Hepatobiliary system
Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see section 4.8). In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued.

Glucose-6-phosphate dehydrogenase deficiency
Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.

Resistance
During or following a course of treatment with ciprofloxacin bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas* species.

Cytochrome P450
Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, ropinirole, tizanidine). Co-administration of ciprofloxacin and tizanidine is contra-indicated. Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5).

Methotrexate
The concomitant use of ciprofloxacin with methotrexate is not recommended (see section 4.5).

Interaction with tests
The *in-vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients currently taking ciprofloxacin.

Injection Site Reaction
Local intravenous site reactions have been reported with the intravenous administration of ciprofloxacin. These reactions are more frequent if the infusion time is 30 minutes or less. These may appear as local skin reactions which resolve rapidly upon completion of the infusion. Subsequent intravenous administration is not contraindicated unless the reactions recur or worsen.

NaCl Load
In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome, etc.), the additional sodium load should be taken into account (for sodium chloride content, see section 2).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on ciprofloxacin:

Probenecid

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.

Effects of ciprofloxacin on other medicinal products:

Tizanidine

Tizanidine must not be administered together with ciprofloxacin (see section 4.3). In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

Theophylline

Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary (see section 4.4).

Other xanthine derivatives

On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivatives were reported.

Phenytoin

Simultaneous administration of ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin such that monitoring of drug levels is recommended.

Oral anticoagulants

Simultaneous administration of ciprofloxacin with warfarin may augment its anti-coagulant effects. There have been many reports of increases in oral anti-coagulant activity in patients receiving antibacterial agents, including fluoroquinolones. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the fluoroquinolone to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anticoagulant agent.

Ropinirole

It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, results in an increase of C_{max} and AUC of ropinirole by 60% and 84%, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin (see section 4.4).

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy
The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism / foetus (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

Lactation
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are nausea, diarrhoea, vomiting, transient increase in transaminases, rash, and injection and infusion site reactions.

ADRs derived from clinical studies and post-marketing surveillance with Ciprofloxacin Bayer (oral, intravenous and sequential therapy) sorted by categories of frequency are listed below. The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin.

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Infections and Infestations		Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4)		

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (life-threatening) (see section 4.4) Serum sickness-like reaction	
Metabolism and Nutrition Disorders		Anorexia	Hyperglycaemia		
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression Hallucinations	Psychotic reactions (see section 4.4)	
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (see section 4.4) Vertigo	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension	Peripheral neuropathy (see section 4.4)
Eye Disorders			Visual disturbances	Visual colour distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss / Hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia, QT prolongation, torsades de pointes *
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Cholestatic icterus Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)	
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions (see section 4.4)	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	
Musculoskeletal, Connective Tissue and Bone Disorders		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) (see section 4.4) Exacerbation of symptoms of myasthenia gravis (see section 4.4)	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria (see section 4.4) Tubulointerstitial nephritis		

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	**Frequency not known** (cannot be estimated from available data)
General Disorders and Administration Site Conditions	Injection and infusion site reactions (only intravenous administration)	Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Prothrombin level abnormal Increased amylase		

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see section 4.4).

The following undesirable effects have a higher frequency category in the subgroups of patients receiving intravenous or sequential (intravenous to oral) treatment:

Common	Vomiting, Transient increase in transaminases, Rash
Uncommon	Thrombocytopenia, Thrombocytaemia, Confusion and disorientation, Hallucinations, Par- and dysaesthesia, Seizures, Vertigo, Visual disturbances, Hearing loss, Tachycardia, Vasodilatation, Hypotension, Transient hepatic impairment, Cholestatic icterus, Renal failure, Oedema
Rare	Pancytopenia, Bone marrow depression, Anaphylactic shock, Psychotic reactions, Migraine, Olfactory nerve disorders, Hearing impaired, Vasculitis, Pancreatitis, Liver necrosis, Petechiae, Tendon rupture

Paediatric patients

The incidence of arthropathy, mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see section 4.4).

4.9 Overdose

An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.
Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has been reported.

Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated. Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02

Mechanism of action:

As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

PK/PD relationship:

Efficacy mainly depends on the relation between the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

Mechanism of resistance:

In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.
Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All *in-vitro* mechanisms of resistance are commonly observed in clinical isolates.
Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to ciprofloxacin.
Plasmid-mediated resistance encoded by qnr-genes has been reported.

Spectrum of antibacterial activity:

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

Microorganisms	Susceptible	Resistant
Enterobacteria	S ≤ 0.5 mg/L	R > 1 mg/L
Pseudomonas	S ≤ 0.5 mg/L	R > 1 mg/L
Acinetobacter	S ≤ 1 mg/L	R > 1 mg/L
Staphylococcus spp.[1]	S ≤ 1 mg/L	R > 1 mg/L
Haemophilus influenzae and Moraxella catarrhalis	S ≤ 0.5 mg/L	R > 0.5 mg/L
Neisseria gonorrhoeae	S ≤ 0.03 mg/L	R > 0.06 mg/L
Neisseria meningitidis	S ≤ 0.03 mg/L	R > 0.06 mg/L
Non-species-related breakpoints*	S ≤ 0.5 mg/L	R > 1 mg/L

1 *Staphylococcus* spp. - breakpoints for ciprofloxacin relate to high dose therapy.
* Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Groupings of relevant species according to ciprofloxacin susceptibility (for *Streptococcus* species see section 4.4)

COMMONLY SUSCEPTIBLE SPECIES

Aerobic Gram-positive micro-organisms *Bacillus anthracis* (1)
Aerobic Gram-negative micro-organisms *Aeromonas* spp. *Brucella* spp. *Citrobacter koseri* *Francisella tularensis* *Haemophilus ducreyi* *Haemophilus influenzae** *Legionella* spp. *Moraxella catarrhalis** *Neisseria meningitidis* *Pasteurella* spp. *Salmonella* spp.* *Shigella* spp. * *Vibrio* spp. *Yersinia pestis*
Anaerobic micro-organisms *Mobiluncus*
Other micro-organisms *Chlamydia trachomatis ($)* *Chlamydia pneumoniae ($)* *Mycoplasma hominis ($)* *Mycoplasma pneumoniae ($)*
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* ($) *Staphylococcus* spp. *(2)
Aerobic Gram-negative micro-organisms *Acinetobacter baumannii*$^{+}$ *Burkholderia cepacia* $^{+}$* *Campylobacter* spp.$^{+}$* *Citrobacter freundii** *Enterobacter aerogenes* *Enterobacter cloacae ** *Escherichia coli** *Klebsiella oxytoca* *Klebsiella pneumoniae** *Morganella morganii** *Neisseria gonorrhoeae** *Proteus mirabilis** *Proteus vulgaris** *Providencia* spp. *Pseudomonas aeruginosa** *Pseudomonas fluorescens* *Serratia marcescens**
Anaerobic micro-organisms *Peptostreptococcus* spp. *Propionibacterium acnes*

INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms *Actinomyces* *Enteroccus faecium* *Listeria monocytogenes*
Aerobic Gram-negative micro-organisms *Stenotrophomonas maltophilia*
Anaerobic micro-organisms Excepted as listed above
Other micro-organisms *Mycoplasma genitalium* *Ureaplasma urealitycum*
* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications + Resistance rate ≥ 50% in one or more EU countries ($): Natural intermediate susceptibility in the absence of acquired mechanism of resistance (1): Studies have been conducted in experimental animal infections due to inhalations of *Bacillus anthracis* spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on *in-vitro* susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and /or international consensus documents regarding treatment of anthrax. (2): Methicillin-resistant *S. aureus* very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.

5.2 Pharmacokinetic properties

Absorption

Following an intravenous infusion of ciprofloxacin the mean maximum serum concentrations were achieved at the end of infusion. Pharmacokinetics of ciprofloxacin were linear over the dose range up to 400 mg administered intravenously.

Comparison of the pharmacokinetic parameters for a twice a day and three times a day intravenous dose regimen indicated no evidence of drug accumulation for ciprofloxacin and its metabolites.

A 60-minute intravenous infusion of 200 mg ciprofloxacin or the oral administration of 250 mg ciprofloxacin, both given every 12 hours, produced an equivalent area under the serum concentration time curve (AUC).

A 60-minute intravenous infusion of 400 mg ciprofloxacin every 12 hours was bioequivalent to a 500 mg oral dose every 12 hours with regard to AUC.

The 400 mg intravenous dose administered over 60 minutes every 12 hours resulted in a C_{max} similar to that observed with a 750 mg oral dose.

A 60-minute infusion of 400 mg ciprofloxacin every 8 hours is equivalent with respect to AUC to 750 mg oral regimen given every 12 hours.

Distribution

Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin

reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Metabolism

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). The metabolites display *in-vitro* antimicrobial activity but to a lower degree than the parent compound.

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally.

Excretion of ciprofloxacin (% of dose)		
	Intravenous Administration	
	Urine	**Faeces**
Ciprofloxacin	61.5	15.2
Metabolites (M_1-M_4)	9.5	2.6

Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half lives of ciprofloxacin of up to 12 h.

Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Paediatric patients

The pharmacokinetic data in paediatric patients are limited.

In a study in children C_{max} and AUC were not age-dependent (above one year of age). No notable increase in C_{max} and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C_{max} was 6.1 mg/L (range 4.6-8.3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.7-11.8 mg/L) for children between 1 and 5 years of age. The AUC values were 17.4 mg*h/L (range 11.8-32.0 mg*h/L) and 16.5 mg*h/L (range 11.0-23.8 mg*h/L) in the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4-5 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction.
Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/ photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin *in-vitro* and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability:
As reported for other gyrase inhibitors, ciprofloxacin causes damage to the large weight-bearing joints in immature animals. The extent of the cartilage damage varies according to age, species and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs, ciprofloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal and other handling

For ease of use the infusion vial stopper should be penetrated in the central ring. Penetration of the outer ring may result in damage to the vial stopper.

Any unused solution should be disposed off.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally.]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally.]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 400 mg/200 mL solution for infusion
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ciprofloxacin Bayer 400 mg/200 mL solution for infusion is indicated for the treatment of the following infections (see sections 4.4 and 5.1). Special attention should be paid to available information on resistance to ciprofloxacin before commencing therapy.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Adults

- Lower respiratory tract infections due to Gram-negative bacteria
  - exacerbations of chronic obstructive pulmonary disease
  - broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
  - pneumonia
- Chronic suppurative otitis media
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
- Urinary tract infections
- Epididymo-orchitis including cases due to *Neisseria gonorrhoeae*
- Pelvic inflammatory disease including cases due to *Neisseria gonorrhoeae*

In the above genital tract infections when thought or known to be due to *Neisseria gonorrhoeae* it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility based on laboratory testing.

- Infections of the gastro-intestinal tract (e.g. travellers` diarrhoea)
- Intra-abdominal infections
- Infections of the skin and soft tissue caused by Gram-negative bacteria
- Malignant external otitis

- Infections of the bones and joints
- Treatment of infections in neutropenic patients
- Prophylaxis of infections in neutropenic patients
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Children and adolescents

- Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*
- Complicated urinary tract infections and pyelonephritis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to be necessary.

Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents (see sections 4.4 and 5.1).

4.2 Posology and method of administration

The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to ciprofloxacin of the causative organism(s), the renal function of the patient and, in children and adolescents the body weight.

The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course.

After intravenous initiation of treatment, the treatment can be switched to oral treatment with tablet or suspension if clinically indicated at the discretion of the physician. IV treatment should be followed by oral route as soon as possible.
In severe cases or if the patient is unable to take tablets (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

Treatment of infections due to certain bacteria (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* or *Staphylococci*) may require higher ciprofloxacin doses and co-administration with other appropriate antibacterial agents.

Treatment of some infections (e.g. pelvic inflammatory disease, intra-abdominal infections, infections in neutropenic patients and infections of bones and joints) may require co-administration with other appropriate antibacterial agents depending on the pathogens involved.

Adults

Indications	**Daily dose in mg**	**Total duration of treatment (including switch to oral therapy as soon as possible)**
Infections of the lower respiratory tract	400 mg twice daily to 400 mg three times a day	7 to 14 days

Indications		**Daily dose in mg**	**Total duration of treatment (including switch to oral therapy as soon as possible)**
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	400 mg twice daily to 400 mg three times a day	7 to 14 days
	Chronic suppurative otitis media	400 mg twice daily to 400 mg three times a day	7 to 14 days
	Malignant external otitis	400 mg three times a day	28 days up to 3 months
Urinary tract infections	Complicated and uncomplicated pyelonephritis	400 mg twice daily to 400 mg three times a day	7 to 21 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Prostatitis	400 mg twice daily to 400 mg three times a day	2 to 4 weeks (acute)
Genital tract infections	Epididymo-orchitis and pelvic inflammatory diseases	400 mg twice daily to 400 mg three times a day	at least 14 days
Infections of the gastro-intestinal tract and intra-abdominal infections	Diarrhoea caused by bacterial pathogens including *Shigella* spp. other than *Shigella dysenteriae* type 1 and empirical treatment of severe travellers' diarrhoea	400 mg twice daily	1 day
	Diarrhoea caused by *Shigella dysenteriae* type 1	400 mg twice daily	5 days
	Diarrhoea caused by *Vibrio cholerae*	400 mg twice daily	3 days
	Typhoid fever	400 mg twice daily	7 days
	Intra-abdominal infections due to Gram-negative bacteria	400 mg twice daily to 400 mg three times a day	5 to 14 days
Infections of the skin and soft tissue		400 mg twice daily to 400 mg three times a day	7 to 14 days
Bone and joint infections		400 mg twice daily to 400 mg three times a day	max. of 3 months
Treatment of infections or prophylaxis of infections in neutropenic patients Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance.		400 mg twice daily to 400 mg three times a day	Therapy should be continued over the entire period of neutropenia

Indications	Daily dose in mg	Total duration of treatment (including switch to oral therapy as soon as possible)
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons requiring parenteral treatment Drug administration should begin as soon as possible after suspected or confirmed exposure.	400 mg twice daily	60 days from the confirmation of *Bacillus anthracis* exposure

Children and adolescents

Indication	Daily dose in mg	Total duration of treatment (including switch to oral therapy as soon as possible)
Cystic fibrosis	10 mg/kg body weight three times a day with a maximum of 400 mg per dose.	10 to 14 days
Complicated urinary tract infections and pyelonephritis	6 mg/kg body weight three times a day to 10 mg/kg body weight three times a day with a maximum of 400 mg per dose.	10 to 21 days
Inhalation anthrax post-exposure curative treatment for persons requiring parenteral treatment Drug administration should begin as soon as possible after suspected or confirmed exposure.	10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 400 mg per dose.	60 days from the confirmation of *Bacillus anthracis* exposure
Other severe infections	10 mg/kg body weight three times a day with a maximum of 400 mg per dose.	According to the type of infections

Geriatric patients

Geriatric patients should receive a dose selected according to the severity of the infection and the patient`s creatinine clearance.

Renal and hepatic impairment

Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance [mL/min/1.73 m²]	Serum Creatinine [µmol/L]	Intravenous Dose [mg]
> 60	< 124	See Usual Dosage.
30-60	124 to 168	200-400 mg every 12 h
< 30	> 169	200-400 mg every 24 h
Patients on haemodialysis	> 169	200-400 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	200-400 mg every 24 h

In patients with impaired liver function no dose adjustment is required.

Dosing in children with impaired renal and/or hepatic function has not been studied.

Method of administration

Ciprofloxacin Bayer should be checked visually prior to use. It must not be used if cloudy.

Ciprofloxacin should be administered by intravenous infusion. For children, the infusion duration is 60 minutes.
In adult patients, infusion time is 60 minutes for 400 mg Ciprofloxacin Bayer and 30 minutes for 200 mg Ciprofloxacin Bayer. Slow infusion into a large vein will minimise patient discomfort and reduce the risk of venous irritation.
The infusion solution can be infused either directly or after mixing with other compatible infusion solutions (see section 6.2).

4.3 Contraindications

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients (see section 6.1).

- Concomitant administration of ciprofloxacin and tizanidine (see section 4.5).

4.4 Special warnings and precautions for use

Severe infections and mixed infections with Gram-positive and anaerobic pathogens
Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections ciprofloxacin must be co-administered with other appropriate antibacterial agents.

Streptococcal Infections (including Streptococcus pneumoniae)
Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Genital tract infections
Epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*. Ciprofloxacin should be co-administered with another appropriate antibacterial agent unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Intra-abdominal infections
There are limited data on the efficacy of ciprofloxacin in the treatment of post-surgical intra-abdominal infections.

Travellers' diarrhoea
The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited.

Infections of the bones and joints
Ciprofloxacin should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation.

Inhalational anthrax
Use in humans is based on *in-vitro* susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and /or international consensus documents regarding the treatment of anthrax.

Children and adolescents
The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. Safety data from a randomised double-blind study on ciprofloxacin use in children (ciprofloxacin: n=335, mean age = 6.3 years; comparators: n=349, mean age = 6.2 years; age range = 1 to 17 years) revealed an incidence of suspected drug-related arthropathy (discerned from joint-related clinical signs and symptoms) by Day +42 of 7.2% and 4.6%. Respectively, an incidence of drug-related arthropathy by 1-year follow-up was 9.0% and 5.7%. The increase of suspected drug-related arthropathy cases over time was not statistically significant between groups. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue.

Broncho-pulmonary infections in cystic fibrosis
Clinical trials have included children and adolescents aged 5-17 years. More limited experience is available in treating children between 1 and 5 years of age.

Complicated urinary tract infections and pyelonephritis
Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.
Clinical trials have included children and adolescents aged 1-17 years.

Other specific severe infections
Other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify a ciprofloxacin use.
The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with these infections.

Hypersensitivity
Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose (see section 4.8) and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.

Musculoskeletal System
Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.

Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, as soon as the first 48 hours of treatment. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids (see section 4.8).
At any sign of tendinitis (e.g. painful swelling, inflammation), ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected limb at rest.
Ciprofloxacin should be used with caution in patients with myasthenia gravis (see section 4.8).

Photosensitivity
Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking ciprofloxacin should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment (see section 4.8).

Central Nervous System
Quinolones are known to trigger seizures or lower the seizure threshold. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued (see section 4.8). Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to self-endangering behaviour. In these cases, ciprofloxacin should be discontinued.
Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving ciprofloxacin. Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see section 4.8).

Cardiac disorders
Since ciprofloxacin is associated with cases of QT prolongation (see section 4.8), caution should be exercised when treating patients at risk for torsades de pointes arrhythmia.

Gastrointestinal System
The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment (see section 4.8). In such cases, ciprofloxacin should immediately be discontinued, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.

Renal and urinary system
Crystalluria related to the use of ciprofloxacin has been reported (see section 4.8). Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

Hepatobiliary system
Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see section 4.8). In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued.

Glucose-6-phosphate dehydrogenase deficiency
Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.

Resistance
During or following a course of treatment with ciprofloxacin bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas species*.

Cytochrome P450
Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, ropinirole, tizanidine). Co-administration of ciprofloxacin and tizanidine is contra-indicated. Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5).

Methotrexate
The concomitant use of ciprofloxacin with methotrexate is not recommended (see section 4.5).

Interaction with tests
The *in-vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients currently taking ciprofloxacin.

Injection Site Reaction
Local intravenous site reactions have been reported with the intravenous administration of ciprofloxacin. These reactions are more frequent if the infusion time is 30 minutes or less. These may appear as local skin reactions which resolve rapidly upon completion of the infusion. Subsequent intravenous administration is not contraindicated unless the reactions recur or worsen.

NaCl Load
In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome, etc.), the additional sodium load should be taken into account (for sodium chloride content, see section 2).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on ciprofloxacin:

Probenecid

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.

Effects of ciprofloxacin on other medicinal products:

Tizanidine

Tizanidine must not be administered together with ciprofloxacin (see section 4.3). In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

Theophylline

Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary (see section 4.4).

Other xanthine derivatives

On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivatives were reported.

Phenytoin

Simultaneous administration of ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin such that monitoring of drug levels is recommended.

Oral anticoagulants

Simultaneous administration of ciprofloxacin with warfarin may augment its anti-coagulant effects. There have been many reports of increases in oral anti-coagulant activity in patients receiving antibacterial agents, including fluoroquinolones. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the fluoroquinolone to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anticoagulant agent.

Ropinirole

It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, results in an increase of C_{max} and AUC of ropinirole by 60% and 84%, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin (see section 4.4).

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy
The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism / foetus (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

Lactation
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are nausea, diarrhoea, vomiting, transient increase in transaminases, rash, and injection and infusion site reactions.

ADRs derived from clinical studies and post-marketing surveillance with Ciprofloxacin Bayer (oral, intravenous and sequential therapy) sorted by categories of frequency are listed below. The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin.

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Infections and Infestations		Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4)		
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (life-threatening) (see section 4.4) Serum sickness-like reaction	
Metabolism and Nutrition Disorders		Anorexia	Hyperglycaemia		
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression Hallucinations	Psychotic reactions (see section 4.4)	
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (see section 4.4) Vertigo	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension	Peripheral neuropathy (see section 4.4)

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Eye Disorders			Visual disturbances	Visual colour distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss / Hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia, QT prolongation, torsades de pointes *
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Cholestatic icterus Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)	
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions (see section 4.4)	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Musculoskeletal, Connective Tissue and Bone Disorders		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) (see section 4.4) Exacerbation of symptoms of myasthenia gravis (see section 4.4)	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria (see section 4.4) Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions	Injection and infusion site reactions (only intravenous administration)	Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Prothrombin level abnormal Increased amylase		

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see section 4.4).

The following undesirable effects have a higher frequency category in the subgroups of patients receiving intravenous or sequential (intravenous to oral) treatment:

Common	Vomiting, Transient increase in transaminases, Rash
Uncommon	Thrombocytopenia, Thrombocytaemia, Confusion and disorientation, Hallucinations, Par- and dysaesthesia, Seizures, Vertigo, Visual disturbances, Hearing loss, Tachycardia, Vasodilatation, Hypotension, Transient hepatic impairment, Cholestatic icterus, Renal failure, Oedema
Rare	Pancytopenia, Bone marrow depression, Anaphylactic shock, Psychotic reactions, Migraine, Olfactory nerve disorders, Hearing impaired, Vasculitis, Pancreatitis, Liver necrosis, Petechiae, Tendon rupture

Paediatric patients

The incidence of arthropathy, mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see section 4.4).

4.9 Overdose

An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.
Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has been reported.

Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated. Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02

Mechanism of action:

As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

PK/PD relationship:

Efficacy mainly depends on the relation between the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

Mechanism of resistance:

In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.
Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All *in-vitro* mechanisms of resistance are commonly observed in clinical isolates.
Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to ciprofloxacin.
Plasmid-mediated resistance encoded by qnr-genes has been reported.

Spectrum of antibacterial activity:

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

Microorganisms	Susceptible	Resistant
Enterobacteria	S ≤ 0.5 mg/L	R > 1 mg/L

Pseudomonas	S ≤ 0.5 mg/L	R > 1 mg/L
Acinetobacter	S ≤ 1 mg/L	R > 1 mg/L
Staphylococcus spp.[1]	S ≤ 1 mg/L	R > 1 mg/L
Haemophilus influenzae and Moraxella catarrhalis	S ≤ 0.5 mg/L	R > 0.5 mg/L
Neisseria gonorrhoeae	S ≤ 0.03 mg/L	R > 0.06 mg/L
Neisseria meningitidis	S ≤ 0.03 mg/L	R > 0.06 mg/L
Non-species-related breakpoints*****	S ≤ 0.5 mg/L	R > 1 mg/L

1 *Staphylococcus* spp. - breakpoints for ciprofloxacin relate to high dose therapy.

* Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Groupings of relevant species according to ciprofloxacin susceptibility (for *Streptococcus* species see section 4.4)

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms *Bacillus anthracis* (1)
Aerobic Gram-negative micro-organisms *Aeromonas* spp. *Brucella* spp. *Citrobacter koseri* *Francisella tularensis* *Haemophilus ducreyi* *Haemophilus influenzae** *Legionella* spp. *Moraxella catarrhalis** *Neisseria meningitidis* *Pasteurella* spp. *Salmonella* spp.* *Shigella* spp. * *Vibrio* spp. *Yersinia pestis*
Anaerobic micro-organisms *Mobiluncus*
Other micro-organisms *Chlamydia trachomatis* ($) *Chlamydia pneumoniae* ($) *Mycoplasma hominis* ($) *Mycoplasma pneumoniae* ($)
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* ($) *Staphylococcus* spp. *(2)

Aerobic Gram-negative micro-organisms *Acinetobacter baumannii*[+] *Burkholderia cepacia* [+]* *Campylobacter* spp.[+]* *Citrobacter freundii** *Enterobacter aerogenes* *Enterobacter cloacae ** *Escherichia coli** *Klebsiella oxytoca* *Klebsiella pneumoniae** *Morganella morganii** *Neisseria gonorrhoeae** *Proteus mirabilis** *Proteus vulgaris** *Providencia* spp. *Pseudomonas aeruginosa** *Pseudomonas fluorescens* *Serratia marcescens**
Anaerobic micro-organisms *Peptostreptococcus* spp. *Propionibacterium acnes*
INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms *Actinomyces* *Enteroccus faecium* *Listeria monocytogenes*
Aerobic Gram-negative micro-organisms *Stenotrophomonas maltophilia*
Anaerobic micro-organisms Excepted as listed above
Other micro-organisms *Mycoplasma genitalium* *Ureaplasma urealitycum*
* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications [+] Resistance rate ≥ 50% in one or more EU countries ($): Natural intermediate susceptibility in the absence of acquired mechanism of resistance (1): Studies have been conducted in experimental animal infections due to inhalations of *Bacillus anthracis* spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on *in-vitro* susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and /or international consensus documents regarding treatment of anthrax. (2): Methicillin-resistant *S. aureus* very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.

5.2 Pharmacokinetic properties

Absorption

Following an intravenous infusion of ciprofloxacin the mean maximum serum concentrations were achieved at the end of infusion. Pharmacokinetics of ciprofloxacin were linear over the dose range up to 400 mg administered intravenously.

Comparison of the pharmacokinetic parameters for a twice a day and three times a day intravenous dose regimen indicated no evidence of drug accumulation for ciprofloxacin and its metabolites.

A 60-minute intravenous infusion of 200 mg ciprofloxacin or the oral administration of 250 mg ciprofloxacin, both given every 12 hours, produced an equivalent area under the serum concentration time curve (AUC).

A 60-minute intravenous infusion of 400 mg ciprofloxacin every 12 hours was bioequivalent to a 500 mg oral dose every 12 hours with regard to AUC.

The 400 mg intravenous dose administered over 60 minutes every 12 hours resulted in a C_{max} similar to that observed with a 750 mg oral dose.

A 60-minute infusion of 400 mg ciprofloxacin every 8 hours is equivalent with respect to AUC to 750 mg oral regimen given every 12 hours.

Distribution

Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Metabolism

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). The metabolites display *in-vitro* antimicrobial activity but to a lower degree than the parent compound.

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally.

Excretion of ciprofloxacin (% of dose)		
	Intravenous Administration	
	Urine	**Faeces**
Ciprofloxacin	61.5	15.2
Metabolites (M_1-M_4)	9.5	2.6

Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half lives of ciprofloxacin of up to 12 h.

Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Paediatric patients

The pharmacokinetic data in paediatric patients are limited.

In a study in children C_{max} and AUC were not age-dependent (above one year of age). No notable increase in C_{max} and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C_{max} was 6.1 mg/L (range 4.6-8.3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.7-11.8 mg/L) for children between 1 and 5 years of age. The AUC values were 17.4 mg*h/L (range 11.8-32.0 mg*h/L) and 16.5 mg*h/L (range 11.0-23.8 mg*h/L) in the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4-5 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction.
Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/ photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin *in-vitro* and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability:
As reported for other gyrase inhibitors, ciprofloxacin causes damage to the large weight-bearing joints in immature animals. The extent of the cartilage damage varies according to age, species and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs, ciprofloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal and other handling

For ease of use the infusion vial stopper should be penetrated in the central ring. Penetration of the outer ring may result in damage to the vial stopper.

Any unused solution should be disposed off.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally.]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally.]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 100 mg film-coated tablets
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 100 mg film-coated tablets
[See Annex I - To be completed nationally]
Ciprofloxacin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

{Name}

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 250 mg film-coated tablets
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 250 mg film-coated tablets
[See Annex I - To be completed nationally]
Ciprofloxacin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

{Name}

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 500 mg film-coated tablets
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 500 mg film-coated tablets
[See Annex I - To be completed nationally]
Ciprofloxacin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

{Name}

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 750 mg film-coated tablets
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 750 mg film-coated tablets
[See Annex I - To be completed nationally]
Ciprofloxacin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

{Name}

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 250 mg oral suspension in single-dose sachets
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Shake before use applying slight pressure to the wall. Then tear the sachet open as indicated and take the contents directly.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SINGLE DOSE SACHETS 250 MG

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ciprofloxacin Bayer and associated names (see Annex I) 250 mg oral suspension in single-dose sachets
[See Annex I - To be completed nationally]
Ciprofloxacin
Oral use

2. METHOD OF ADMINISTRATION

Shake before use applying slight pressure to the wall. Then tear the sachet open as indicated and take the contents directly.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

[To be completed nationally]

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 500 mg oral suspension in single-dose sachets
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Shake before use applying slight pressure to the wall. Then tear the sachet open as indicated and take the contents directly.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SINGLE DOSE SACHETS 500 MG

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ciprofloxacin Bayer and associated names (see Annex I) 500 mg oral suspension in single-dose sachets
[See Annex I - To be completed nationally]
Ciprofloxacin
Oral use

2. METHOD OF ADMINISTRATION

Shake before use applying slight pressure to the wall. Then tear the sachet open as indicated and take the contents directly.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

[To be completed nationally]

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON
50 mg/mL ORAL SUSPENSION (containing the bottle(s) for the granules and the bottle(s) for the solvent)

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 50 mg/mL granules and solvent for oral suspension
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Only after reconstitution
Shake well before use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

GLASS BOTTLE 50 mg/mL

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 50 mg/mL granules for oral suspension
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Only after reconstitution
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

HDPE BOTTLE 50 mg/mL

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 50 mg/mL solvent for oral suspension
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Only after reconstitution
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON
100 mg/mL ORAL SUSPENSION (containing the bottle(s) for the granules and the bottle(s) for the solvent)

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 100 mg/mL granules and solvent for oral suspension
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Only after reconstitution
Shake well before use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

GLASS BOTTLE 100 mg/mL

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 100 mg/mL granules for oral suspension
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Only after reconstitution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

HDPE BOTTLE 100 mg/mL

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 100 mg/mL solvent for oral suspension
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Only after reconstitution
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (containing wraps with bags of 100 mL solution for infusion)

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 200 mg / 100 mL solution for infusion
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAP (containing 1 infusion bag of 200 mg / 100 mL solution for infusion)

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 200 mg / 100 mL solution for infusion
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

FLEXIBLE PO/PVC BAG (200 mg / 100 mL solution for infusion)

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 200 mg / 100 mL solution for infusion
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally.]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (containing wraps with bags of 200 mL solution for infusion)

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 400 mg / 200 mL solution for infusion
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAP (containing 1 infusion bag of 400 mg / 200 mL solution for infusion)

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 400 mg / 200 mL solution for infusion
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

FLEXIBLE PO/PVC BAG (400 mg / 200 mL solution for infusion)

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 400 mg / 200 mL solution for infusion
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (containing 5 boxes with bottles of 50 mL solution for infusion)

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 100 mg / 50 mL solution for infusion
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (containing 1 bottle of 100 mg / 50 mL solution for infusion)

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 100 mg / 50 mL solution for infusion
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

COLOURLESS TYPE-2 GLASS BOTTLE WITH GREY SILICONISED BROMOBUTYL STOPPER OR CHLOROBUTYL STOPPER

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 100 mg / 50 mL solution for infusion
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (containing 5 or 40 boxes with bottles of 100 mL solution for infusion)

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 200 mg/100 mL solution for infusion
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (containing 1 bottle of 200 mg / 100 mL solution for infusion)

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 200 mg/100 mL solution for infusion
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

COLOURLESS TYPE-2 GLASS BOTTLE WITH GREY SILICONISED BROMOBUTYL STOPPER OR CHLOROBUTYL STOPPER

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 200 mg/100 mL solution for infusion
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (containing 5 boxes with bottles of 200 mL solution for infusion)

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 400 mg/200 mL solution for infusion
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (containing 1 bottle of 400 mg /200 mL solution for infusion)

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 400 mg/200 mL solution for infusion
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

COLOURLESS TYPE-2 GLASS BOTTLE WITH GREY SILICONISED BROMOBUTYL STOPPER OR CHLOROBUTYL STOPPER.

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Bayer and associated names (see Annex I) 400 mg/200 mL solution for infusion
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ciprofloxacin Bayer and associated names (see Annex I) 100 mg film-coated tablets
[See Annex I - To be completed nationally]

Ciprofloxacin

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT CIPROFLOXACIN BAYER IS AND WHAT IT IS USED FOR

Ciprofloxacin Bayer is an antibiotic belonging to the fluoroquinolone family. The active substance is ciprofloxacin. Ciprofloxacin works by killing bacteria that cause infections. It only works with specific strains of bacteria.

Adults

Ciprofloxacin Bayer is used in adults to treat the following bacterial infections:

- respiratory tract infections
- long lasting or recurring ear or sinus infections
- urinary tract infections
- infections of the testicles
- genital organ infections in women
- gastro-intestinal tract infections and intra-abdominal infections
- skin and soft tissue infections
- bone and joint infections
- to treat infections in patients with a very low white blood cell count (neutropenia)
- to prevent infections in patients with a very low white blood cell count (neutropenia)
- to prevent infections due to the bacterium *Neisseria meningitidis*
- anthrax inhalation exposure

If you have a severe infection or one that is caused by more than one type of bacterium, you may be given additional antibiotic treatment in addition to Ciprofloxacin Bayer.

Children and adolescents

Ciprofloxacin Bayer is used in children and adolescents, under specialist medical supervision, to treat the following bacterial infections:

- lung and bronchial infections in children and adolescents suffering from cystic fibrosis
- complicated urinary tract infections, including infections that have reached the kidneys (pyelonephritis)
- anthrax inhalation exposure

Ciprofloxacin Bayer may also be used to treat other specific severe infections in children and adolescents when your doctor considered this necessary.

2. BEFORE YOU TAKE CIPROFLOXACIN BAYER

Do not take Ciprofloxacin Bayer if you are:

- allergic (hypersensitive) to the active substance, to other quinolone drugs or to any of the other ingredients of Ciprofloxacin Bayer (see section 6)
- taking tizanidine (see Section 2: Taking other medicines)

Take special care with Ciprofloxacin Bayer

Before taking Ciprofloxacin Bayer

Tell your doctor if you:

- have ever had kidney problems because your treatment may need to be adjusted
- suffer from epilepsy or other neurological conditions
- have a history of tendon problems during previous treatment with antibiotics such as Ciprofloxacin Bayer
- have myasthenia gravis (a type of muscle weakness)
- have a history of abnormal heart rhythms (arrythmias)

While taking Ciprofloxacin Bayer

Tell your doctor immediately, if any of the following occurs **while taking Ciprofloxacin Bayer**. Your doctor will decide whether treatment with Ciprofloxacin Bayer needs to be stopped.

- **Severe, sudden allergic reaction** (an anaphylactic reaction/shock, angio-oedema). Even with the first dose, there is a small chance that you may experience a severe allergic reaction with the following symptoms: tightness in the chest, feeling dizzy, sick or faint, or experiencing dizziness when standing up. **If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.**

- **Pain and swelling in the joints and tendinitis** may occur occasionally, particularly if you are elderly and are also being treated with corticosteroids. At the first sign of any pain or inflammation stop taking Ciprofloxacin Bayer and rest the painful area. Avoid any unnecessary exercise, as this might increase the risk of a tendon rupture.

- If you suffer from **epilepsy** or other **neurological conditions** such as cerebral ischemia or stroke, you may experience side effects associated with the central nervous system. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience **psychiatric reactions** the first time you take Ciprofloxacin Bayer. If you suffer from **depression** or **psychosis**, your symptoms may become worse under treatment with Ciprofloxacin Bayer. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience symptoms of neuropathy such as pain, burning, tingling, numbness and/or weakness. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- **Diarrhoea** may develop while you are taking antibiotics, including Ciprofloxacin Bayer, or even several weeks after you have stopped taking them. If it becomes severe or persistent or you notice that your stool contains blood or mucus, stop taking Ciprofloxacin Bayer immediately, as this can be life-threatening. Do not take medicines that stop or slow down bowel movements and contact your doctor.

- Tell the doctor or laboratory staff that you are taking Ciprofloxacin Bayer if you have to provide a **blood or urine sample**.

- Ciprofloxacin Bayer may cause **liver damage**. If you notice any symptoms such as loss of appetite, jaundice (yellowing of the skin), dark urine, itching, or tenderness of the stomach, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- Ciprofloxacin Bayer may cause a reduction in the number of white blood cells and your **resistance to infection may be decreased**. If you experience an infection with symptoms such as fever and serious deterioration of your general condition, or fever with local infection symptoms such as sore throat/pharynx/mouth or urinary problems you should see your doctor immediately. A blood test will be taken to check possible reduction of white blood cells (agranulocytosis). It is important to inform your doctor about your medicine.

- Tell your doctor if you or a member of your family is known to have a deficiency in glucose-6-phosphate dehydrogenase (G6PD), since you may experience a risk of anemia with ciprofloxacin.

- Your skin becomes more **sensitive to sunlight or ultraviolet (UV) light** when taking Ciprofloxacin Bayer. Avoid exposure to strong sunlight, or artificial UV light such as sunbeds.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including any that you obtained without a prescription.

Do not take Ciprofloxacin Bayer together with tizanidine, because this may cause side effects such as low blood pressure and sleepiness (see Section 2: "Do not take Ciprofloxacin Bayer").

The following medicines are known to interact with Ciprofloxacin Bayer in your body. Taking Ciprofloxacin Bayer together with these medicines can influence the therapeutic effect of those medicines. It can also increase the probability of experiencing side effects.

Tell your doctor if you are taking:

- warfarin or other oral anti-coagulants (to thin the blood)
- probenecid (for gout)
- methotrexate (for certain types of cancer, psoriasis, rheumatoid arthritis)
- theophylline (for breathing problems)
- tizanidine (for muscle spasticity in multiple sclerosis)
- clozapine (an antipsychotic)
- ropinirole (for Parkinson’s disease)
- phenytoin (for epilepsy)

Ciprofloxacin Bayer may **increase** the levels of the following medicines in your blood:

- pentoxifylline (for circulatory disorders)
- caffeine

Some medicines **reduce** the effect of Ciprofloxacin Bayer. Tell your doctor if you take or wish to take:

- antacids
- mineral supplements
- sucralfate
- a polymeric phosphate binder (e.g. sevelamer)
- medicines or supplements containing calcium, magnesium, aluminium or iron

If these preparations are essential, take Ciprofloxacin Bayer about two hours before or no sooner than four hours after them.

Taking Ciprofloxacin Bayer with food and drink

Unless you take Ciprofloxacin Bayer during meals, do not eat or drink any dairy products (such as milk or yoghurt) or drinks with added calcium when you take the tablets, as they may affect the absorption of the active substance.

Pregnancy and breast-feeding

It is preferable to avoid the use of Ciprofloxacin Bayer during pregnancy. Tell your doctor if you are planning to get pregnant.

Do not take Ciprofloxacin Bayer during breast feeding because ciprofloxacin is excreted in breast milk and can be harmful for your child.

Driving and using machines

Ciprofloxacin Bayer may make you feel less alert. Some neurological adverse events can occur. Therefore, make sure you know how you react to Ciprofloxacin Bayer before driving a vehicle or operating machinery. If in doubt, talk to your doctor.

3. HOW TO TAKE CIPROFLOXACIN BAYER

Your doctor will explain to you exactly how much Ciprofloxacin Bayer you will have to take as well as how often and for how long. This will depend on the type of infection you have and how bad it is.

Tell your doctor if you suffer from kidney problems because your dose may need to be adjusted.

The treatment usually lasts from 5 to 21 days, but may take longer for severe infections. Take the tablets exactly as your doctor has told you. Ask your doctor or pharmacist if you are not sure how many tablets to take and how to take Ciprofloxacin Bayer.

a. Swallow the tablets with plenty of fluid. Do not chew the tablets because they do not taste nice.
b. Do try to take the tablets at around the same time every day.
c. You can take the tablets at mealtimes or between meals. Any calcium you take as part of a meal will not seriously affect uptake. However, **do not** take Ciprofloxacin Bayer tablets with dairy products such as milk or yoghurt or with fortified fruit-juices (e.g. calcium-fortified orange juice).

Remember to drink plenty of fluids while you are taking Ciprofloxacin Bayer.

If you take more Ciprofloxacin Bayer than you should

- If you take more than the prescribed dose, get medical help immediately. If possible, take your tablets or the box with you to show the doctor.

If you forget to take Ciprofloxacin Bayer

- Take the normal dose as soon as possible and then continue as prescribed. However, if it is almost time for your next dose, do not take the missed dose and continue as usual. Do not take a double dose to make up for a forgotten dose. Be sure to complete your course of treatment.

If you stop taking Ciprofloxacin Bayer

- It is important that you **finish the course of treatment** even if you begin to feel better after a few days. If you stop taking this medicine too soon, your infection may not be completely cured and the symptoms of the infection may return or get worse. You might also develop resistance to the antibiotic.

If you have any more questions about the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ciprofloxacin Bayer can cause side effects, although not everybody gets them.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

Common side effects (between 1 and 10 in every 100 people are likely to get these):

- nausea, diarrhoea
- joint pains in children

Uncommon side effects (between 1 and 10 in every 1,000 people are likely to get these):

- fungal superinfections
- a high concentration of eosinophils, a type of white blood cell
- loss of appetite (anorexia)
- hyperactivity or agitation
- headache, dizziness, sleeping problems, or taste disorders
- vomiting, abdominal pain, digestive problems such as stomach upset (indigestion/heartburn), or wind
- increased amounts of certain substances in the blood (transaminases and/or bilirubin)
- rash, itching, or hives
- joint pain in adults
- poor kidney function
- pains in your muscles and bones, feeling unwell (asthenia), or fever
- increase in blood alkaline phosphatase (a certain substance in the blood)

Rare side effects (between 1 and 10 in every 10,000 people are likely to get these):

- inflammation of the bowel (colitis) linked to antibiotic use (can be fatal in very rare cases) (see Section 2: Take special care with Ciprofloxacin Bayer)
- changes to the blood count (leukopenia, leukocytosis, neutropenia, anaemia), increased or decreased amounts of a blood clotting factor (thrombocytes)
- allergic reaction, swelling (oedema), or rapid swelling of the skin and mucous membranes (angio-oedema)
- increased blood sugar (hyperglycaemia)
- confusion, disorientation, anxiety reactions, strange dreams, depression, or hallucinations

- pins and needles, unusual sensitivity to stimuli of the senses, decreased skin sensitivity, tremors, seizures (see Section 2: Take special care with Ciprofloxacin Bayer), or giddiness
- eyesight problems
- tinnitus, loss of hearing, impaired hearing
- rapid heartbeat (tachycardia)
- expansion of blood vessels (vasodilation), low blood pressure, or fainting
- shortness of breath, including asthmatic symptoms
- liver disorders, jaundice (cholestatic icterus), or hepatitis
- sensitivity to light (see Section 2: Take special care with Ciprofloxacin Bayer)
- muscle pain, inflammation of the joints, increased muscle tone, or cramp
- kidney failure, blood or crystals in the urine (see Section 2: Take special care with Ciprofloxacin Bayer), urinary tract inflammation
- fluid retention or excessive sweating
- abnormal levels of a clotting factor (prothrombin) or increased levels of the enzyme amylase

Very rare side effects (less than 1 in every 10,000 people are likely to get these):

- a special type of reduced red blood cell count (haemolytic anaemia); a dangerous drop in a type of white blood cells (agranulocytosis); a drop in the number of red and white blood cells and platelets (pancytopenia), which may be fatal; and bone marrow depression, which may also be fatal (see Section 2: Take special care with Ciprofloxacin Bayer)
- severe allergic reactions (anaphylactic reaction or anaphylactic shock, which can be fatal - serum sickness) (see Section 2: Take special care with Ciprofloxacin Bayer)
- mental disturbances (psychotic reactions) (see Section 2: Take special care with Ciprofloxacin Bayer)
- migraine, disturbed coordination, unsteady walk (gait disturbance), disorder of sense of smell (olfactory disorders), pressure on the brain (intracranial pressure)
- visual colour distortions
- inflammation of the wall of the blood vessels (vasculitis)
- pancreatitis
- death of liver cells (liver necrosis) very rarely leading to life-threatening liver failure
- small, pin-point bleeding under the skin (petechiae); various skin eruptions or rashes (for example, the potentially fatal Stevens-Johnson syndrome or toxic epidermal necrolysis)
- muscle weakness, tendon inflammation, tendon rupture – especially of the large tendon at the back of the ankle (Achilles tendon) (see Section 2: Take special care with Ciprofloxacin Bayer); worsening of the symptoms of myasthenia gravis (see Section 2: Take special care with Ciprofloxacin Bayer)

Frequency not known (cannot be estimated from the available data)
- troubles associated with the nervous system such as pain, burning, tingling, numbness and/or weakness in extremities
- severe cardiac rhythm abnormalities, irregular heart beat (Torsades de Pointes)

5. HOW TO STORE CIPROFLOXACIN BAYER

[To be completed nationally]

Keep out of the reach and sight of children.

Do not use Ciprofloxacin Bayer after the expiry date, which is stated on the blister or carton after "EXP": The expiry date refers to the last day of the month concerned.

Medicines should not be disposed of down the drain or with household rubbish. Ask your pharmacist how to dispose of any medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ciprofloxacin Bayer contains

[To be completed nationally]

What Ciprofloxacin Bayer looks like and contents of the pack

Film-coated tablet
[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

Belgium:	Ciproxine
Czech Republic:	Ciprobay Uro
Germany:	Ciprobay Uro
Ireland:	Ciproxin
Luxembourg:	Ciproxine
Netherlands:	Ciproxin
Poland:	Ciprobay Uro
United Kingdom:	Ciproxin

This leaflet was last approved in {MM/YYYY}

[To be completed nationally]

Advice/medical education

Antibiotics are used to cure bacterial infections. They are ineffective against viral infections.
If your doctor has prescribed antibiotics, you need them precisely for your current illness.
Despite antibiotics, some bacteria may survive or grow. This phenomenon is called resistance: some antibiotic treatments become ineffective.
Misuse of antibiotics increases resistance. You may even help bacteria become resistant and therefore delay your cure or decrease antibiotic efficacy if you do not respect appropriate:
- dosages
- schedules
- duration of treatment

Consequently, to preserve the efficacy of this drug:
1 - Use antibiotics only when prescribed.
2 - Strictly follow the prescription.
3 - Do not re-use an antibiotic without medical prescription, even if you want to treat a similar illness.
4 - Never give your antibiotic to another person; maybe it is not adapted to her/his illness.
5 - After completion of treatment, return all unused drugs to your chemist's shop to ensure they will be disposed of correctly.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ciprofloxacin Bayer and associated names (see Annex I) 250 mg film-coated tablets
[See Annex I - To be completed nationally]

Ciprofloxacin

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
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- gastro-intestinal tract infections and intra-abdominal infections
- skin and soft tissue infections
- bone and joint infections
- to treat infections in patients with a very low white blood cell count (neutropenia)
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- to prevent infections due to the bacterium *Neisseria meningitidis*
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Take special care with Ciprofloxacin Bayer

Before taking Ciprofloxacin Bayer

Tell your doctor if you:

- have ever had kidney problems because your treatment may need to be adjusted
- suffer from epilepsy or other neurological conditions
- have a history of tendon problems during previous treatment with antibiotics such as Ciprofloxacin Bayer
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While taking Ciprofloxacin Bayer

Tell your doctor immediately, if any of the following occurs **while taking Ciprofloxacin Bayer**. Your doctor will decide whether treatment with Ciprofloxacin Bayer needs to be stopped.

- **Severe, sudden allergic reaction** (an anaphylactic reaction/shock, angio-oedema). Even with the first dose, there is a small chance that you may experience a severe allergic reaction with the following symptoms: tightness in the chest, feeling dizzy, sick or faint, or experiencing dizziness when standing up. **If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.**

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- **Diarrhoea** may develop while you are taking antibiotics, including Ciprofloxacin Bayer, or even several weeks after you have stopped taking them. If it becomes severe or persistent or you notice that your stool contains blood or mucus, stop taking Ciprofloxacin Bayer immediately, as this can be life-threatening. Do not take medicines that stop or slow down bowel movements and contact your doctor.

- Tell the doctor or laboratory staff that you are taking Ciprofloxacin Bayer if you have to provide a **blood or urine sample**.

- Ciprofloxacin Bayer may cause **liver damage**. If you notice any symptoms such as loss of appetite, jaundice (yellowing of the skin), dark urine, itching, or tenderness of the stomach, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

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- Tell your doctor if you or a member of your family is known to have a deficiency in glucose-6-phosphate dehydrogenase (G6PD), since you may experience a risk of anemia with ciprofloxacin.

- Your skin becomes more **sensitive to sunlight or ultraviolet (UV) light** when taking Ciprofloxacin Bayer. Avoid exposure to strong sunlight, or artificial UV light such as sunbeds.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including any that you obtained without a prescription.

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- methotrexate (for certain types of cancer, psoriasis, rheumatoid arthritis)
- theophylline (for breathing problems)
- tizanidine (for muscle spasticity in multiple sclerosis)
- clozapine (an antipsychotic)
- ropinirole (for Parkinson’s disease)
- phenytoin (for epilepsy)

Ciprofloxacin Bayer may **increase** the levels of the following medicines in your blood:

- pentoxifylline (for circulatory disorders)
- caffeine

Some medicines **reduce** the effect of Ciprofloxacin Bayer. Tell your doctor if you take or wish to take:

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- a polymeric phosphate binder (e.g. sevelamer)
- medicines or supplements containing calcium, magnesium, aluminium or iron

If these preparations are essential, take Ciprofloxacin Bayer about two hours before or no sooner than four hours after them.

Taking Ciprofloxacin Bayer with food and drink

Unless you take Ciprofloxacin Bayer during meals, do not eat or drink any dairy products (such as milk or yoghurt) or drinks with added calcium when you take the tablets, as they may affect the absorption of the active substance.

Pregnancy and breast-feeding

It is preferable to avoid the use of Ciprofloxacin Bayer during pregnancy. Tell your doctor if you are planning to get pregnant.

Do not take Ciprofloxacin Bayer during breast feeding because ciprofloxacin is excreted in breast milk and can be harmful for your child.

Driving and using machines

Ciprofloxacin Bayer may make you feel less alert. Some neurological adverse events can occur. Therefore, make sure you know how you react to Ciprofloxacin Bayer before driving a vehicle or operating machinery. If in doubt, talk to your doctor.

3. HOW TO TAKE CIPROFLOXACIN BAYER

Your doctor will explain to you exactly how much Ciprofloxacin Bayer you will have to take as well as how often and for how long. This will depend on the type of infection you have and how bad it is.

Tell your doctor if you suffer from kidney problems because your dose may need to be adjusted.

The treatment usually lasts from 5 to 21 days, but may take longer for severe infections. Take the tablets exactly as your doctor has told you. Ask your doctor or pharmacist if you are not sure how many tablets to take and how to take Ciprofloxacin Bayer.

a. Swallow the tablets with plenty of fluid. Do not chew the tablets because they do not taste nice.
b. Do try to take the tablets at around the same time every day.
c. You can take the tablets at mealtimes or between meals. Any calcium you take as part of a meal will not seriously affect uptake. However, **do not** take Ciprofloxacin Bayer tablets with dairy products such as milk or yoghurt or with fortified fruit juices (e.g. calcium-fortified orange juice).

Remember to drink plenty of fluids while you are taking Ciprofloxacin Bayer.

If you take more Ciprofloxacin Bayer than you should

- If you take more than the prescribed dose, get medical help immediately. If possible, take your tablets or the box with you to show the doctor.

If you forget to take Ciprofloxacin Bayer

- Take the normal dose as soon as possible and then continue as prescribed. However, if it is almost time for your next dose, do not take the missed dose and continue as usual. Do not take a double dose to make up for a forgotten dose. Be sure to complete your course of treatment.

If you stop taking Ciprofloxacin Bayer

- It is important that you **finish the course of treatment** even if you begin to feel better after a few days. If you stop taking this medicine too soon, your infection may not be completely cured and the symptoms of the infection may return or get worse. You might also develop resistance to the antibiotic.

If you have any more questions about the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ciprofloxacin Bayer can cause side effects, although not everybody gets them.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

Common side effects (between 1 and 10 in every 100 people are likely to get these):

- nausea, diarrhoea
- joint pains in children

Uncommon side effects (between 1 and 10 in every 1,000 people are likely to get these):

- fungal superinfections
- a high concentration of eosinophils, a type of white blood cell
- loss of appetite (anorexia)
- hyperactivity or agitation
- headache, dizziness, sleeping problems, or taste disorders
- vomiting, abdominal pain, digestive problems such as stomach upset (indigestion/heartburn), or wind
- increased amounts of certain substances in the blood (transaminases and/or bilirubin)
- rash, itching, or hives
- joint pain in adults
- poor kidney function
- pains in your muscles and bones, feeling unwell (asthenia), or fever
- increase in blood alkaline phosphatase (a certain substance in the blood)

Rare side effects (between 1 and 10 in every 10,000 people are likely to get these):

- inflammation of the bowel (colitis) linked to antibiotic use (can be fatal in very rare cases) (see Section 2: Take special care with Ciprofloxacin Bayer)
- changes to the blood count (leukopenia, leukocytosis, neutropenia, anaemia), increased or decreased amounts of a blood clotting factor (thrombocytes)
- allergic reaction, swelling (oedema), or rapid swelling of the skin and mucous membranes (angio-oedema)
- increased blood sugar (hyperglycaemia)
- confusion, disorientation, anxiety reactions, strange dreams, depression, or hallucinations

- pins and needles, unusual sensitivity to stimuli of the senses, decreased skin sensitivity, tremors, seizures (see Section 2: Take special care with Ciprofloxacin Bayer), or giddiness
- eyesight problems
- tinnitus, loss of hearing, impaired hearing
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- expansion of blood vessels (vasodilation), low blood pressure, or fainting
- shortness of breath, including asthmatic symptoms
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- sensitivity to light (see Section 2: Take special care with Ciprofloxacin Bayer)
- muscle pain, inflammation of the joints, increased muscle tone, or cramp
- kidney failure, blood or crystals in the urine (see Section 2: Take special care with Ciprofloxacin Bayer), urinary tract inflammation
- fluid retention or excessive sweating
- abnormal levels of a clotting factor (prothrombin) or increased levels of the enzyme amylase

Very rare side effects (less than 1 in every 10,000 people are likely to get these):

- a special type of reduced red blood cell count (haemolytic anaemia); a dangerous drop in a type of white blood cells (agranulocytosis); a drop in the number of red and white blood cells and platelets (pancytopenia), which may be fatal; and bone marrow depression, which may also be fatal (see Section 2: Take special care with Ciprofloxacin Bayer)
- severe allergic reactions (anaphylactic reaction or anaphylactic shock, which can be fatal - serum sickness) (see Section 2: Take special care with Ciprofloxacin Bayer)
- mental disturbances (psychotic reactions) (see Section 2: Take special care with Ciprofloxacin Bayer)
- migraine, disturbed coordination, unsteady walk (gait disturbance), disorder of sense of smell (olfactory disorders), pressure on the brain (intracranial pressure)
- visual colour distortions
- inflammation of the wall of the blood vessels (vasculitis)
- pancreatitis
- death of liver cells (liver necrosis) very rarely leading to life-threatening liver failure
- small, pin-point bleeding under the skin (petechiae); various skin eruptions or rashes (for example, the potentially fatal Stevens-Johnson syndrome or toxic epidermal necrolysis)
- muscle weakness, tendon inflammation, tendon rupture – especially of the large tendon at the back of the ankle (Achilles tendon) (see Section 2: Take special care with Ciprofloxacin Bayer); worsening of the symptoms of myasthenia gravis (see Section 2: Take special care with Ciprofloxacin Bayer)

Frequency not known (cannot be estimated from the available data)
- troubles associated with the nervous system such as pain, burning, tingling, numbness and/or weakness in extremities
- severe cardiac rhythm abnormalities, irregular heart beat (Torsades de Pointes)

5. HOW TO STORE CIPROFLOXACIN BAYER

[To be completed nationally]

Keep out of the reach and sight of children.

Do not use Ciprofloxacin Bayer after the expiry date, which is stated on the blister or carton after "EXP": The expiry date refers to the last day of the month concerned.

Medicines should not be disposed of down the drain or with household rubbish. Ask your pharmacist how to dispose of any medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ciprofloxacin Bayer contains

[To be completed nationally]

What Ciprofloxacin Bayer looks like and contents of the pack

Film-coated tablet
[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria:	Ciproxin
Belgium:	Ciproxine
Bulgaria:	Ciprobay
Cyprus:	Ciproxin
Czech Republic:	Ciprobay
Denmark:	Ciproxin
Estonia:	Ciproxin
Finland:	Ciproxin
France:	Ciflox
Germany:	Ciprobay; Ciprofloxacin ANTIBAC
Hungary:	Ciprobay
Iceland:	Ciproxin
Ireland:	Ciproxin
Italy:	Ciflox; Ciproxin
Luxembourg:	Ciproxine
Malta:	Ciproxin
Netherlands:	Ciproxin
Norway:	Ciproxin
Poland:	Ciprobay
Portugal:	Ciproxina
Slovac Republic:	Ciprobay
Slovenia:	Ciprobay
Spain:	Baycip
Sweden:	Ciproxin
United Kingdom:	Ciproxin

This leaflet was last approved in {MM/YYYY}

[To be completed nationally]

Advice/medical education

Antibiotics are used to cure bacterial infections. They are ineffective against viral infections.
If your doctor has prescribed antibiotics, you need them precisely for your current illness.
Despite antibiotics, some bacteria may survive or grow. This phenomenon is called resistance: some antibiotic treatments become ineffective.
Misuse of antibiotics increases resistance. You may even help bacteria become resistant and therefore delay your cure or decrease antibiotic efficacy if you do not respect appropriate:

- dosages
- schedules
- duration of treatment

Consequently, to preserve the efficacy of this drug:

1 - Use antibiotics only when prescribed.
2 - Strictly follow the prescription.
3 - Do not re-use an antibiotic without medical prescription, even if you want to treat a similar illness.
4 - Never give your antibiotic to another person; maybe it is not adapted to her/his illness.
5 - After completion of treatment, return all unused drugs to your chemist's shop to ensure they will be disposed of correctly.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ciprofloxacin Bayer and associated names (see Annex I) 500 mg film-coated tablets
[See Annex I - To be completed nationally]

Ciprofloxacin

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT CIPROFLOXACIN BAYER IS AND WHAT IT IS USED FOR

Ciprofloxacin Bayer is an antibiotic belonging to the fluoroquinolone family. The active substance is ciprofloxacin. Ciprofloxacin works by killing bacteria that cause infections. It only works with specific strains of bacteria.

Adults

Ciprofloxacin Bayer is used in adults to treat the following bacterial infections:

- respiratory tract infections
- long lasting or recurring ear or sinus infections
- urinary tract infections
- infections of the testicles
- genital organ infections in women
- gastro-intestinal tract infections and intra-abdominal infections
- skin and soft tissue infections
- bone and joint infections
- to treat infections in patients with a very low white blood cell count (neutropenia)
- to prevent infections in patients with a very low white blood cell count (neutropenia)
- to prevent infections due to the bacterium *Neisseria meningitidis*
- anthrax inhalation exposure

If you have a severe infection or one that is caused by more than one type of bacterium, you may be given additional antibiotic treatment in addition to Ciprofloxacin Bayer.

Children and adolescents

Ciprofloxacin Bayer is used in children and adolescents, under specialist medical supervision, to treat the following bacterial infections:

- lung and bronchial infections in children and adolescents suffering from cystic fibrosis
- complicated urinary tract infections, including infections that have reached the kidneys (pyelonephritis)
- anthrax inhalation exposure

Ciprofloxacin Bayer may also be used to treat other specific severe infections in children and adolescents when your doctor considered this necessary.

2. BEFORE YOU TAKE CIPROFLOXACIN BAYER

Do not take Ciprofloxacin Bayer if you are:

- allergic (hypersensitive) to the active substance, to other quinolone drugs or to any of the other ingredients of Ciprofloxacin Bayer (see section 6)
- taking tizanidine (see Section 2: Taking other medicines)

Take special care with Ciprofloxacin Bayer

Before taking Ciprofloxacin Bayer

Tell your doctor if you:

- have ever had kidney problems because your treatment may need to be adjusted
- suffer from epilepsy or other neurological conditions
- have a history of tendon problems during previous treatment with antibiotics such as Ciprofloxacin Bayer
- have myasthenia gravis (a type of muscle weakness)
- have a history of abnormal heart rhythms (arrythmias)

While taking Ciprofloxacin Bayer

Tell your doctor immediately, if any of the following occurs **while taking Ciprofloxacin Bayer**. Your doctor will decide whether treatment with Ciprofloxacin Bayer needs to be stopped.

- **Severe, sudden allergic reaction** (an anaphylactic reaction/shock, angio-oedema). Even with the first dose, there is a small chance that you may experience a severe allergic reaction with the following symptoms: tightness in the chest, feeling dizzy, sick or faint, or experiencing dizziness when standing up. **If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.**

- **Pain and swelling in the joints and tendinitis** may occur occasionally, particularly if you are elderly and are also being treated with corticosteroids. At the first sign of any pain or inflammation stop taking Ciprofloxacin Bayer and rest the painful area. Avoid any unnecessary exercise, as this might increase the risk of a tendon rupture.

- If you suffer from **epilepsy** or other **neurological conditions** such as cerebral ischemia or stroke, you may experience side effects associated with the central nervous system. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience **psychiatric reactions** the first time you take Ciprofloxacin Bayer. If you suffer from **depression** or **psychosis**, your symptoms may become worse under treatment with Ciprofloxacin Bayer. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience symptoms of neuropathy such as pain, burning, tingling, numbness and/or weakness. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- **Diarrhoea** may develop while you are taking antibiotics, including Ciprofloxacin Bayer, or even several weeks after you have stopped taking them. If it becomes severe or persistent or you notice that your stool contains blood or mucus, stop taking Ciprofloxacin Bayer immediately, as this can be life-threatening. Do not take medicines that stop or slow down bowel movements and contact your doctor.

- Tell the doctor or laboratory staff that you are taking Ciprofloxacin Bayer if you have to provide a **blood or urine sample**.

- Ciprofloxacin Bayer may cause **liver damage**. If you notice any symptoms such as loss of appetite, jaundice (yellowing of the skin), dark urine, itching, or tenderness of the stomach, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- Ciprofloxacin Bayer may cause a reduction in the number of white blood cells and your **resistance to infection may be decreased**. If you experience an infection with symptoms such as fever and serious deterioration of your general condition, or fever with local infection symptoms such as sore throat/pharynx/mouth or urinary problems you should see your doctor immediately. A blood test will be taken to check possible reduction of white blood cells (agranulocytosis). It is important to inform your doctor about your medicine.

- Tell your doctor if you or a member of your family is known to have a deficiency in glucose-6-phosphate dehydrogenase (G6PD), since you may experience a risk of anemia with ciprofloxacin.

- Your skin becomes more **sensitive to sunlight or ultraviolet (UV) light** when taking Ciprofloxacin Bayer. Avoid exposure to strong sunlight, or artificial UV light such as sunbeds.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including any that you obtained without a prescription.

Do not take Ciprofloxacin Bayer together with tizanidine, because this may cause side effects such as low blood pressure and sleepiness (see Section 2: "Do not take Ciprofloxacin Bayer").

The following medicines are known to interact with Ciprofloxacin Bayer in your body. Taking Ciprofloxacin Bayer together with these medicines can influence the therapeutic effect of those medicines. It can also increase the probability of experiencing side effects.

Tell your doctor if you are taking:

- warfarin or other oral anti-coagulants (to thin the blood)
- probenecid (for gout)
- methotrexate (for certain types of cancer, psoriasis, rheumatoid arthritis)
- theophylline (for breathing problems)
- tizanidine (for muscle spasticity in multiple sclerosis)
- clozapine (an antipsychotic)
- ropinirole (for Parkinson’s disease)
- phenytoin (for epilepsy)

Ciprofloxacin Bayer may **increase** the levels of the following medicines in your blood:

- pentoxifylline (for circulatory disorders)
- caffeine

Some medicines **reduce** the effect of Ciprofloxacin Bayer. Tell your doctor if you take or wish to take:

- antacids
- mineral supplements
- sucralfate
- a polymeric phosphate binder (e.g. sevelamer)
- medicines or supplements containing calcium, magnesium, aluminium or iron

If these preparations are essential, take Ciprofloxacin Bayer about two hours before or no sooner than four hours after them.

Taking Ciprofloxacin Bayer with food and drink

Unless you take Ciprofloxacin Bayer during meals, do not eat or drink any dairy products (such as milk or yoghurt) or drinks with added calcium when you take the tablets, as they may affect the absorption of the active substance.

Pregnancy and breast-feeding

It is preferable to avoid the use of Ciprofloxacin Bayer during pregnancy. Tell your doctor if you are planning to get pregnant.

Do not take Ciprofloxacin Bayer during breast feeding because ciprofloxacin is excreted in breast milk and can be harmful for your child.

Driving and using machines

Ciprofloxacin Bayer may make you feel less alert. Some neurological adverse events can occur. Therefore, make sure you know how you react to Ciprofloxacin Bayer before driving a vehicle or operating machinery. If in doubt, talk to your doctor.

3. HOW TO TAKE CIPROFLOXACIN BAYER

Your doctor will explain to you exactly how much Ciprofloxacin Bayer you will have to take as well as how often and for how long. This will depend on the type of infection you have and how bad it is.

Tell your doctor if you suffer from kidney problems because your dose may need to be adjusted.

The treatment usually lasts from 5 to 21 days, but may take longer for severe infections. Take the tablets exactly as your doctor has told you. Ask your doctor or pharmacist if you are not sure how many tablets to take and how to take Ciprofloxacin Bayer.

a. Swallow the tablets with plenty of fluid. Do not chew the tablets because they do not taste nice.
b. Do try to take the tablets at around the same time every day.
c. You can take the tablets at mealtimes or between meals. Any calcium you take as part of a meal will not seriously affect uptake. However, **do not** take Ciprofloxacin Bayer tablets with dairy products such as milk or yoghurt or with fortified fruit juices (e.g. calcium-fortified orange juice).

Remember to drink plenty of fluids while you are taking Ciprofloxacin Bayer.

If you take more Ciprofloxacin Bayer than you should

- If you take more than the prescribed dose, get medical help immediately. If possible, take your tablets or the box with you to show the doctor.

If you forget to take Ciprofloxacin Bayer

- Take the normal dose as soon as possible and then continue as prescribed. However, if it is almost time for your next dose, do not take the missed dose and continue as usual. Do not take a double dose to make up for a forgotten dose. Be sure to complete your course of treatment.

If you stop taking Ciprofloxacin Bayer

- It is important that you **finish the course of treatment** even if you begin to feel better after a few days. If you stop taking this medicine too soon, your infection may not be completely cured and the symptoms of the infection may return or get worse. You might also develop resistance to the antibiotic.

If you have any more questions about the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ciprofloxacin Bayer can cause side effects, although not everybody gets them.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

Common side effects (between 1 and 10 in every 100 people are likely to get these):

- nausea, diarrhoea
- joint pains in children

Uncommon side effects (between 1 and 10 in every 1,000 people are likely to get these):

- fungal superinfections
- a high concentration of eosinophils, a type of white blood cell
- loss of appetite (anorexia)
- hyperactivity or agitation
- headache, dizziness, sleeping problems, or taste disorders
- vomiting, abdominal pain, digestive problems such as stomach upset (indigestion/heartburn), or wind
- increased amounts of certain substances in the blood (transaminases and/or bilirubin)
- rash, itching, or hives
- joint pain in adults
- poor kidney function
- pains in your muscles and bones, feeling unwell (asthenia), or fever
- increase in blood alkaline phosphatase (a certain substance in the blood)

Rare side effects (between 1 and 10 in every 10,000 people are likely to get these):

- inflammation of the bowel (colitis) linked to antibiotic use (can be fatal in very rare cases) (see Section 2: Take special care with Ciprofloxacin Bayer)
- changes to the blood count (leukopenia, leukocytosis, neutropenia, anaemia), increased or decreased amounts of a blood clotting factor (thrombocytes)
- allergic reaction, swelling (oedema), or rapid swelling of the skin and mucous membranes (angio-oedema)
- increased blood sugar (hyperglycaemia)
- confusion, disorientation, anxiety reactions, strange dreams, depression, or hallucinations

- pins and needles, unusual sensitivity to stimuli of the senses, decreased skin sensitivity, tremors, seizures (see Section 2: Take special care with Ciprofloxacin Bayer), or giddiness
- eyesight problems
- tinnitus, loss of hearing, impaired hearing
- rapid heartbeat (tachycardia)
- expansion of blood vessels (vasodilation), low blood pressure, or fainting
- shortness of breath, including asthmatic symptoms
- liver disorders, jaundice (cholestatic icterus), or hepatitis
- sensitivity to light (see Section 2: Take special care with Ciprofloxacin Bayer)
- muscle pain, inflammation of the joints, increased muscle tone, or cramp
- kidney failure, blood or crystals in the urine (see Section 2: Take special care with Ciprofloxacin Bayer), urinary tract inflammation
- fluid retention or excessive sweating
- abnormal levels of a clotting factor (prothrombin) or increased levels of the enzyme amylase

Very rare side effects (less than 1 in every 10,000 people are likely to get these):

- a special type of reduced red blood cell count (haemolytic anaemia); a dangerous drop in a type of white blood cells (agranulocytosis); a drop in the number of red and white blood cells and platelets (pancytopenia), which may be fatal; and bone marrow depression, which may also be fatal (see Section 2: Take special care with Ciprofloxacin Bayer)
- severe allergic reactions (anaphylactic reaction or anaphylactic shock, which can be fatal - serum sickness) (see Section 2: Take special care with Ciprofloxacin Bayer)
- mental disturbances (psychotic reactions) (see Section 2: Take special care with Ciprofloxacin Bayer)
- migraine, disturbed coordination, unsteady walk (gait disturbance), disorder of sense of smell (olfactory disorders), pressure on the brain (intracranial pressure)
- visual colour distortions
- inflammation of the wall of the blood vessels (vasculitis)
- pancreatitis
- death of liver cells (liver necrosis) very rarely leading to life-threatening liver failure
- small, pin-point bleeding under the skin (petechiae); various skin eruptions or rashes (for example, the potentially fatal Stevens-Johnson syndrome or toxic epidermal necrolysis)
- muscle weakness, tendon inflammation, tendon rupture – especially of the large tendon at the back of the ankle (Achilles tendon) (see Section 2: Take special care with Ciprofloxacin Bayer); worsening of the symptoms of myasthenia gravis (see Section 2: Take special care with Ciprofloxacin Bayer)

Frequency not known (cannot be estimated from the available data)
- troubles associated with the nervous system such as pain, burning, tingling, numbness and/or weakness in extremities
- severe cardiac rhythm abnormalities, irregular heart beat (Torsades de Pointes)

5. HOW TO STORE CIPROFLOXACIN BAYER

[To be completed nationally]

Keep out of the reach and sight of children.

Do not use Ciprofloxacin Bayer after the expiry date, which is stated on the blister or carton after "EXP": The expiry date refers to the last day of the month concerned.

Medicines should not be disposed of down the drain or with household rubbish. Ask your pharmacist how to dispose of any medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ciprofloxacin Bayer contains

[To be completed nationally]

What Ciprofloxacin Bayer looks like and contents of the pack

Film-coated tablet
[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria:	Ciproxin
Belgium:	Ciproxine
Bulgaria:	Ciprobay
Cyprus:	Ciproxin
Czech Republic:	Ciprobay
Denmark:	Ciproxin
Estonia:	Ciproxin
Finland:	Ciproxin
France:	Ciflox; Uniflox
Germany:	Ciprobay; Ciprofloxacin ANTIBAC
Greece:	Ciproxin
Hungary:	Ciprobay
Iceland:	Ciproxin
Ireland:	Ciproxin
Italy:	Ciflox; Ciproxin
Luxembourg:	Ciproxine
Malta:	Ciproxin
Netherlands:	Ciproxin
Norway:	Ciproxin
Poland:	Ciprobay
Portugal:	Ciproxina
Romania:	Ciprobay
Slovac Republic:	Ciprobay
Slovenia:	Ciprobay
Spain:	Baycip
Sweden:	Ciproxin
United Kingdom:	Ciproxin

This leaflet was last approved in {MM/YYYY}

[To be completed nationally]

Advice/medical education

Antibiotics are used to cure bacterial infections. They are ineffective against viral infections.
If your doctor has prescribed antibiotics, you need them precisely for your current illness.
Despite antibiotics, some bacteria may survive or grow. This phenomenon is called resistance: some antibiotic treatments become ineffective.
Misuse of antibiotics increases resistance. You may even help bacteria become resistant and therefore delay your cure or decrease antibiotic efficacy if you do not respect appropriate:

- dosages
- schedules
- duration of treatment

Consequently, to preserve the efficacy of this drug:

1 - Use antibiotics only when prescribed.
2 - Strictly follow the prescription.
3 - Do not re-use an antibiotic without medical prescription, even if you want to treat a similar illness.
4 - Never give your antibiotic to another person; maybe it is not adapted to her/his illness.
5 - After completion of treatment, return all unused drugs to your chemist's shop to ensure they will be disposed of correctly.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ciprofloxacin Bayer and associated names (see Annex I) 750 mg film-coated tablets
[See Annex I - To be completed nationally]

Ciprofloxacin

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT CIPROFLOXACIN BAYER IS AND WHAT IT IS USED FOR

Ciprofloxacin Bayer is an antibiotic belonging to the fluoroquinolone family. The active substance is ciprofloxacin. Ciprofloxacin works by killing bacteria that cause infections. It only works with specific strains of bacteria.

Adults

Ciprofloxacin Bayer is used in adults to treat the following bacterial infections:

- respiratory tract infections
- long lasting or recurring ear or sinus infections
- urinary tract infections
- infections of the testicles
- genital organ infections in women
- gastro-intestinal tract infections and intra-abdominal infections
- skin and soft tissue infections
- bone and joint infections
- to treat infections in patients with a very low white blood cell count (neutropenia)
- to prevent infections in patients with a very low white blood cell count (neutropenia)
- to prevent infections due to the bacterium *Neisseria meningitidis*
- anthrax inhalation exposure

If you have a severe infection or one that is caused by more than one type of bacterium, you may be given additional antibiotic treatment in addition to Ciprofloxacin Bayer.

Children and adolescents

Ciprofloxacin Bayer is used in children and adolescents, under specialist medical supervision, to treat the following bacterial infections:

- lung and bronchial infections in children and adolescents suffering from cystic fibrosis
- complicated urinary tract infections, including infections that have reached the kidneys (pyelonephritis)
- anthrax inhalation exposure

Ciprofloxacin Bayer may also be used to treat other specific severe infections in children and adolescents when your doctor considered this necessary.

2. BEFORE YOU TAKE CIPROFLOXACIN BAYER

Do not take Ciprofloxacin Bayer if you are:

- allergic (hypersensitive) to the active substance, to other quinolone drugs or to any of the other ingredients of Ciprofloxacin Bayer (see section 6)
- taking tizanidine (see Section 2: Taking other medicines)

Take special care with Ciprofloxacin Bayer

Before taking Ciprofloxacin Bayer

Tell your doctor if you:

- have ever had kidney problems because your treatment may need to be adjusted
- suffer from epilepsy or other neurological conditions
- have a history of tendon problems during previous treatment with antibiotics such as Ciprofloxacin Bayer
- have myasthenia gravis (a type of muscle weakness)
- have a history of abnormal heart rhythms (arrythmias)

While taking Ciprofloxacin Bayer

Tell your doctor immediately, if any of the following occurs **while taking Ciprofloxacin Bayer**. Your doctor will decide whether treatment with Ciprofloxacin Bayer needs to be stopped.

- **Severe, sudden allergic reaction** (an anaphylactic reaction/shock, angio-oedema). Even with the first dose, there is a small chance that you may experience a severe allergic reaction with the following symptoms: tightness in the chest, feeling dizzy, sick or faint, or experiencing dizziness when standing up. **If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately**.

- **Pain and swelling in the joints and tendinitis** may occur occasionally, particularly if you are elderly and are also being treated with corticosteroids. At the first sign of any pain or inflammation stop taking Ciprofloxacin Bayer and rest the painful area. Avoid any unnecessary exercise, as this might increase the risk of a tendon rupture.

- If you suffer from **epilepsy** or other **neurological conditions** such as cerebral ischemia or stroke, you may experience side effects associated with the central nervous system. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience **psychiatric reactions** the first time you take Ciprofloxacin Bayer. If you suffer from **depression** or **psychosis**, your symptoms may become worse under treatment with Ciprofloxacin Bayer. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience symptoms of neuropathy such as pain, burning, tingling, numbness and/or weakness. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- **Diarrhoea** may develop while you are taking antibiotics, including Ciprofloxacin Bayer, or even several weeks after you have stopped taking them. If it becomes severe or persistent or you notice that your stool contains blood or mucus, stop taking Ciprofloxacin Bayer immediately, as this can be life-threatening. Do not take medicines that stop or slow down bowel movements and contact your doctor.

- Tell the doctor or laboratory staff that you are taking Ciprofloxacin Bayer if you have to provide a **blood or urine sample**.

- Ciprofloxacin Bayer may cause **liver damage**. If you notice any symptoms such as loss of appetite, jaundice (yellowing of the skin), dark urine, itching, or tenderness of the stomach, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- Ciprofloxacin Bayer may cause a reduction in the number of white blood cells and your **resistance to infection may be decreased**. If you experience an infection with symptoms such as fever and serious deterioration of your general condition, or fever with local infection symptoms such as sore throat/pharynx/mouth or urinary problems you should see your doctor immediately. A blood test will be taken to check possible reduction of white blood cells (agranulocytosis). It is important to inform your doctor about your medicine.

- Tell your doctor if you or a member of your family is known to have a deficiency in glucose-6-phosphate dehydrogenase (G6PD), since you may experience a risk of anemia with ciprofloxacin.

- Your skin becomes more **sensitive to sunlight or ultraviolet (UV) light** when taking Ciprofloxacin Bayer. Avoid exposure to strong sunlight, or artificial UV light such as sunbeds.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including any that you obtained without a prescription.

Do not take Ciprofloxacin Bayer together with tizanidine, because this may cause side effects such as low blood pressure and sleepiness (see Section 2: "**Do not take Ciprofloxacin Bayer**").

The following medicines are known to interact with Ciprofloxacin Bayer in your body. Taking Ciprofloxacin Bayer together with these medicines can influence the therapeutic effect of those medicines. It can also increase the probability of experiencing side effects.

Tell your doctor if you are taking:

- warfarin or other oral anti-coagulants (to thin the blood)
- probenecid (for gout)
- methotrexate (for certain types of cancer, psoriasis, rheumatoid arthritis)
- theophylline (for breathing problems)
- tizanidine (for muscle spasticity in multiple sclerosis)
- clozapine (an antipsychotic)
- ropinirole (for Parkinson's disease)
- phenytoin (for epilepsy)

Ciprofloxacin Bayer may **increase** the levels of the following medicines in your blood:

- pentoxifylline (for circulatory disorders)
- caffeine

Some medicines **reduce** the effect of Ciprofloxacin Bayer**.** Tell your doctor if you take or wish to take:

- antacids
- mineral supplements
- sucralfate
- a polymeric phosphate binder (e.g. sevelamer)
- medicines or supplements containing calcium, magnesium, aluminium or iron

If these preparations are essential, take Ciprofloxacin Bayer about two hours before or no sooner than four hours after them.

Taking Ciprofloxacin Bayer with food and drink

Unless you take Ciprofloxacin Bayer during meals, do not eat or drink any dairy products (such as milk or yoghurt) or drinks with added calcium when you take the tablets, as they may affect the absorption of the active substance.

Pregnancy and breast-feeding

It is preferable to avoid the use of Ciprofloxacin Bayer during pregnancy. Tell your doctor if you are planning to get pregnant.

Do not take Ciprofloxacin Bayer during breast feeding because ciprofloxacin is excreted in breast milk and can be harmful for your child.

Driving and using machines

Ciprofloxacin Bayer may make you feel less alert. Some neurological adverse events can occur. Therefore, make sure you know how you react to Ciprofloxacin Bayer before driving a vehicle or operating machinery. If in doubt, talk to your doctor.

3. HOW TO TAKE CIPROFLOXACIN BAYER

Your doctor will explain to you exactly how much Ciprofloxacin Bayer you will have to take as well as how often and for how long. This will depend on the type of infection you have and how bad it is.

Tell your doctor if you suffer from kidney problems because your dose may need to be adjusted.

The treatment usually lasts from 5 to 21 days, but may take longer for severe infections. Take the tablets exactly as your doctor has told you. Ask your doctor or pharmacist if you are not sure how many tablets to take and how to take Ciprofloxacin Bayer.

a. Swallow the tablets with plenty of fluid. Do not chew the tablets because they do not taste nice.
b. Do try to take the tablets at around the same time every day.
c. You can take the tablets at mealtimes or between meals. Any calcium you take as part of a meal will not seriously affect uptake. However, **do not** take Ciprofloxacin Bayer tablets with dairy products such as milk or yoghurt or with fortified fruit juices (e.g. calcium-fortified orange juice).

Remember to drink plenty of fluids while you are taking Ciprofloxacin Bayer.

If you take more Ciprofloxacin Bayer than you should

- If you take more than the prescribed dose, get medical help immediately. If possible, take your tablets or the box with you to show the doctor.

If you forget to take Ciprofloxacin Bayer

- Take the normal dose as soon as possible and then continue as prescribed. However, if it is almost time for your next dose, do not take the missed dose and continue as usual. Do not take a double dose to make up for a forgotten dose. Be sure to complete your course of treatment.

If you stop taking Ciprofloxacin Bayer

- It is important that you **finish the course of treatment** even if you begin to feel better after a few days. If you stop taking this medicine too soon, your infection may not be completely cured and the symptoms of the infection may return or get worse. You might also develop resistance to the antibiotic.

If you have any more questions about the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ciprofloxacin Bayer can cause side effects, although not everybody gets them.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

Common side effects (between 1 and 10 in every 100 people are likely to get these):

- nausea, diarrhoea
- joint pains in children

Uncommon side effects (between 1 and 10 in every 1,000 people are likely to get these):

- fungal superinfections
- a high concentration of eosinophils, a type of white blood cell
- loss of appetite (anorexia)
- hyperactivity or agitation
- headache, dizziness, sleeping problems, or taste disorders
- vomiting, abdominal pain, digestive problems such as stomach upset (indigestion/heartburn), or wind
- increased amounts of certain substances in the blood (transaminases and/or bilirubin)
- rash, itching, or hives
- joint pain in adults
- poor kidney function
- pains in your muscles and bones, feeling unwell (asthenia), or fever
- increase in blood alkaline phosphatase (a certain substance in the blood)

Rare side effects (between 1 and 10 in every 10,000 people are likely to get these):

- inflammation of the bowel (colitis) linked to antibiotic use (can be fatal in very rare cases) (see Section 2: Take special care with Ciprofloxacin Bayer)
- changes to the blood count (leukopenia, leukocytosis, neutropenia, anaemia), increased or decreased amounts of a blood clotting factor (thrombocytes)

- allergic reaction, swelling (oedema), or rapid swelling of the skin and mucous membranes (angio-oedema)
- increased blood sugar (hyperglycaemia)
- confusion, disorientation, anxiety reactions, strange dreams, depression, or hallucinations
- pins and needles, unusual sensitivity to stimuli of the senses, decreased skin sensitivity, tremors, seizures (see Section 2: Take special care with Ciprofloxacin Bayer), or giddiness
- eyesight problems
- tinnitus, loss of hearing, impaired hearing
- rapid heartbeat (tachycardia)
- expansion of blood vessels (vasodilation), low blood pressure, or fainting
- shortness of breath, including asthmatic symptoms
- liver disorders, jaundice (cholestatic icterus), or hepatitis
- sensitivity to light (see Section 2: Take special care with Ciprofloxacin Bayer)
- muscle pain, inflammation of the joints, increased muscle tone, or cramp
- kidney failure, blood or crystals in the urine (see Section 2: Take special care with Ciprofloxacin Bayer), urinary tract inflammation
- fluid retention or excessive sweating
- abnormal levels of a clotting factor (prothrombin) or increased levels of the enzyme amylase

Very rare side effects (less than 1 in every 10,000 people are likely to get these):

- a special type of reduced red blood cell count (haemolytic anaemia); a dangerous drop in a type of white blood cells (agranulocytosis); a drop in the number of red and white blood cells and platelets (pancytopenia), which may be fatal; and bone marrow depression, which may also be fatal (see Section 2: Take special care with Ciprofloxacin Bayer)
- severe allergic reactions (anaphylactic reaction or anaphylactic shock, which can be fatal - serum sickness) (see Section 2: Take special care with Ciprofloxacin Bayer)
- mental disturbances (psychotic reactions) (see Section 2: Take special care with Ciprofloxacin Bayer)
- migraine, disturbed coordination, unsteady walk (gait disturbance), disorder of sense of smell (olfactory disorders), pressure on the brain (intracranial pressure)
- visual colour distortions
- inflammation of the wall of the blood vessels (vasculitis)
- pancreatitis
- death of liver cells (liver necrosis) very rarely leading to life-threatening liver failure
- small, pin-point bleeding under the skin (petechiae); various skin eruptions or rashes (for example, the potentially fatal Stevens-Johnson syndrome or toxic epidermal necrolysis)
- muscle weakness, tendon inflammation, tendon rupture – especially of the large tendon at the back of the ankle (Achilles tendon) (see Section 2: Take special care with Ciprofloxacin Bayer); worsening of the symptoms of myasthenia gravis (see Section 2: Take special care with Ciprofloxacin Bayer)

Frequency not known (cannot be estimated from the available data)
- troubles associated with the nervous system such as pain, burning, tingling, numbness and/or weakness in extremities
- severe cardiac rhythm abnormalities, irregular heart beat (Torsades de Pointes)

5. HOW TO STORE CIPROFLOXACIN BAYER

[To be completed nationally]

Keep out of the reach and sight of children.

Do not use Ciprofloxacin Bayer after the expiry date, which is stated on the blister or carton after "EXP": The expiry date refers to the last day of the month concerned.

Medicines should not be disposed of down the drain or with household rubbish. Ask your pharmacist how to dispose of any medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ciprofloxacin Bayer contains

[To be completed nationally]

What Ciprofloxacin Bayer looks like and contents of the pack

Film-coated tablet
[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria:	Ciproxin
Belgium:	Ciproxine
Czech Republic:	Ciprobay
Denmark:	Ciproxin
Finland:	Ciproxin
France:	Ciflox
Germany:	Ciprobay; Ciprofloxacin ANTIBAC
Greece:	Ciproxin
Iceland:	Ciproxin
Ireland:	Ciproxin
Italy:	Ciproxin
Luxembourg:	Ciproxine
Netherlands:	Ciproxin
Norway:	Ciproxin
Portugal:	Ciproxina
Slovac Republic:	Ciprobay
Slovenia:	Ciprobay
Spain:	Baycip
Sweden:	Ciproxin
United Kingdom:	Ciproxin

This leaflet was last approved in {MM/YYYY}

[To be completed nationally]

Advice/medical education

Antibiotics are used to cure bacterial infections. They are ineffective against viral infections.
If your doctor has prescribed antibiotics, you need them precisely for your current illness.

Despite antibiotics, some bacteria may survive or grow. This phenomenon is called resistance: some antibiotic treatments become ineffective.
Misuse of antibiotics increases resistance. You may even help bacteria become resistant and therefore delay your cure or decrease antibiotic efficacy if you do not respect appropriate:

- dosages
- schedules
- duration of treatment

Consequently, to preserve the efficacy of this drug:

1 - Use antibiotics only when prescribed.
2 - Strictly follow the prescription.
3 - Do not re-use an antibiotic without medical prescription, even if you want to treat a similar illness.
4 - Never give your antibiotic to another person; maybe it is not adapted to her/his illness.
5 - After completion of treatment, return all unused drugs to your chemist's shop to ensure they will be disposed of correctly.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ciprofloxacin Bayer and associated names (see Annex I) 250 mg oral suspension in single-dose sachets
[See Annex I - To be completed nationally]

Ciprofloxacin

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT CIPROFLOXACIN BAYER IS AND WHAT IT IS USED FOR

Ciprofloxacin Bayer is an antibiotic belonging to the fluoroquinolone family. The active substance is ciprofloxacin. Ciprofloxacin works by killing bacteria that cause infections. It only works with specific strains of bacteria.

Adults

Ciprofloxacin Bayer is used in adults to treat the following bacterial infections:

- respiratory tract infections
- long lasting or recurring ear or sinus infections
- urinary tract infections
- infections of the testicles
- genital organ infections in women
- gastro-intestinal tract infections and intra-abdominal infections
- skin and soft tissue infections
- bone and joint infections
- to treat infections in patients with a very low white blood cell count (neutropenia)
- to prevent infections in patients with a very low white blood cell count (neutropenia)
- to prevent infections due to the bacterium *Neisseria meningitidis*
- anthrax inhalation exposure

If you have a severe infection or one that is caused by more than one type of bacterium, you may be given additional antibiotic treatment in addition to Ciprofloxacin Bayer.

Children and adolescents

Ciprofloxacin Bayer is used in children and adolescents, under specialist medical supervision, to treat the following bacterial infections:

- lung and bronchial infections in children and adolescents suffering from cystic fibrosis
- complicated urinary tract infections, including infections that have reached the kidneys (pyelonephritis)
- anthrax inhalation exposure

Ciprofloxacin Bayer may also be used to treat other specific severe infections in children and adolescents when your doctor considered this necessary.

2. BEFORE YOU TAKE CIPROFLOXACIN BAYER

Do not take Ciprofloxacin Bayer if you are:

- allergic (hypersensitive) to the active substance, to other quinolone drugs or to any of the other ingredients of Ciprofloxacin Bayer (see section 6)
- taking tizanidine (see Section 2: Taking other medicines)

Take special care with Ciprofloxacin Bayer

Before taking Ciprofloxacin Bayer

Tell your doctor if you:

- have ever had kidney problems because your treatment may need to be adjusted
- suffer from epilepsy or other neurological conditions
- have a history of tendon problems during previous treatment with antibiotics such as Ciprofloxacin Bayer
- have myasthenia gravis (a type of muscle weakness)
- have a history of abnormal heart rhythms (arrythmias)

While taking Ciprofloxacin Bayer

Tell your doctor immediately, if any of the following occurs **while taking Ciprofloxacin Bayer**. Your doctor will decide whether treatment with Ciprofloxacin Bayer needs to be stopped.

- **Severe, sudden allergic reaction** (an anaphylactic reaction/shock, angio-oedema). Even with the first dose, there is a small chance that you may experience a severe allergic reaction with the following symptoms: tightness in the chest, feeling dizzy, sick or faint, or experiencing dizziness when standing up. **If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.**

- **Pain and swelling in the joints and tendinitis** may occur occasionally, particularly if you are elderly and are also being treated with corticosteroids. At the first sign of any pain or inflammation stop taking Ciprofloxacin Bayer and rest the painful area. Avoid any unnecessary exercise, as this might increase the risk of a tendon rupture.

- If you suffer from **epilepsy** or other **neurological conditions** such as cerebral ischemia or stroke, you may experience side effects associated with the central nervous system. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience **psychiatric reactions** the first time you take Ciprofloxacin Bayer. If you suffer from **depression** or **psychosis**, your symptoms may become worse under treatment with Ciprofloxacin Bayer. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience symptoms of neuropathy such as pain, burning, tingling, numbness and/or weakness. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- **Diarrhoea** may develop while you are taking antibiotics, including Ciprofloxacin Bayer, or even several weeks after you have stopped taking them. If it becomes severe or persistent or you notice that your stool contains blood or mucus, stop taking Ciprofloxacin Bayer immediately, as this can be life-threatening. Do not take medicines that stop or slow down bowel movements and contact your doctor.

- Tell the doctor or laboratory staff that you are taking Ciprofloxacin Bayer if you have to provide a **blood or urine sample.**

- Ciprofloxacin Bayer may cause **liver damage**. If you notice any symptoms such as loss of appetite, jaundice (yellowing of the skin), dark urine, itching, or tenderness of the stomach, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- Ciprofloxacin Bayer may cause a reduction in the number of white blood cells and your **resistance to infection may be decreased**. If you experience an infection with symptoms such as fever and serious deterioration of your general condition, or fever with local infection symptoms such as sore throat/pharynx/mouth or urinary problems you should see your doctor immediately. A blood test will be taken to check possible reduction of white blood cells (agranulocytosis). It is important to inform your doctor about your medicine.

- Tell your doctor if you or a member of your family is known to have a deficiency in glucose-6-phosphate dehydrogenase (G6PD), since you may experience a risk of anemia with ciprofloxacin.

- Your skin becomes more **sensitive to sunlight or ultraviolet (UV) light** when taking Ciprofloxacin Bayer. Avoid exposure to strong sunlight, or artificial UV light such as sunbeds.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including any that you obtained without a prescription.

Do not take Ciprofloxacin Bayer together with tizanidine, because this may cause side effects such as low blood pressure and sleepiness (see Section 2: "Do not take Ciprofloxacin Bayer").

The following medicines are known to interact with Ciprofloxacin Bayer in your body. Taking Ciprofloxacin Bayer together with these medicines can influence the therapeutic effect of those medicines. It can also increase the probability of experiencing side effects.

Tell your doctor if you are taking:

- warfarin or other oral anti-coagulants (to thin the blood)
- probenecid (for gout)
- methotrexate (for certain types of cancer, psoriasis, rheumatoid arthritis)
- theophylline (for breathing problems)
- tizanidine (for muscle spasticity in multiple sclerosis)
- clozapine (an antipsychotic)

- ropinirole (for Parkinson's disease)
- phenytoin (for epilepsy)

Ciprofloxacin Bayer may **increase** the levels of the following medicines in your blood:

- pentoxifylline (for circulatory disorders)
- caffeine

Some medicines **reduce** the effect of Ciprofloxacin Bayer. Tell your doctor if you take or wish to take:

- antacids
- mineral supplements
- sucralfate
- a polymeric phosphate binder (e.g. sevelamer)
- medicines or supplements containing calcium, magnesium, aluminium or iron

If these preparations are essential, take Ciprofloxacin Bayer about two hours before or no sooner than four hours after them.

Taking Ciprofloxacin Bayer with food and drink

Unless you take Ciprofloxacin Bayer during meals, do not eat or drink any dairy products (such as milk or yoghurt) or drinks with added calcium when you take the suspension, as they may affect the absorption of the active substance.

Pregnancy and breast-feeding

It is preferable to avoid the use of Ciprofloxacin Bayer during pregnancy. Tell your doctor if you are planning to get pregnant.

Do not take Ciprofloxacin Bayer during breast feeding because ciprofloxacin is excreted in breast milk and can be harmful for your child.

Driving and using machines

Ciprofloxacin Bayer may make you feel less alert. Some neurological adverse events can occur. Therefore, make sure you know how you react to Ciprofloxacin Bayer before driving a vehicle or operating machinery. If in doubt, talk to your doctor.

3. HOW TO TAKE CIPROFLOXACIN BAYER

Your doctor will explain to you exactly how much Ciprofloxacin Bayer you will have to take as well as how often and for how long. This will depend on the type of infection you have and how bad it is.

Tell your doctor if you suffer from kidney problems because your dose may need to be adjusted.

The treatment usually lasts from 5 to 21 days, but may take longer for severe infections. Take the suspension exactly as your doctor has told you. Ask your doctor or pharmacist if you are not sure how many sachets to take and how to take Ciprofloxacin Bayer.

Taking the suspension

Shake the sachet applying slight pressure to the walls. Then tear the sachet open as indicated and take the contents directly.

You can take the sachets at mealtimes or in between meals. Any calcium you take as part of a meal will not seriously affect uptake. However, **do not** take Ciprofloxacin Bayer suspension with dairy products such as milk or yoghurt or with fortified fruit-juice (e.g. calcium-fortified orange-juice)

Remember to drink plenty of fluids while you are taking Ciprofloxacin Bayer.

Do try to take the sachet at around the same time every day.

If you take more Ciprofloxacin Bayer than you should

- If you take more than the prescribed dose, get medical help immediately. If possible, take the sachets or the box with you to show the doctor.

If you forget to take Ciprofloxacin Bayer

- Take the normal dose as soon as possible and then continue as prescribed. However, if it is almost time for your next dose, do not take the missed dose and continue as usual. Do not take a double dose to make up for a forgotten dose. Be sure to complete your course of treatment.

If you stop taking Ciprofloxacin Bayer

- It is important that you **finish the course of treatment** even if you begin to feel better after a few days. If you stop taking this medicine too soon, your infection may not be completely cured and the symptoms of the infection may return or get worse. You might also develop resistance to the antibiotic.

If you have any more questions about the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ciprofloxacin Bayer can cause side effects, although not everybody gets them.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

Common side effects (between 1 and 10 in every 100 people are likely to get these):

- nausea, diarrhoea
- joint pains in children

Uncommon side effects (between 1 and 10 in every 1,000 people are likely to get these):

- fungal superinfections
- a high concentration of eosinophils, a type of white blood cell
- loss of appetite (anorexia)
- hyperactivity or agitation
- headache, dizziness, sleeping problems, or taste disorders
- vomiting, abdominal pain, digestive problems such as stomach upset (indigestion/heartburn), or wind
- increased amounts of certain substances in the blood (transaminases and/or bilirubin)
- rash, itching, or hives
- joint pain in adults
- poor kidney function
- pains in your muscles and bones, feeling unwell (asthenia), or fever
- increase in blood alkaline phosphatase (a certain substance in the blood)

Rare side effects (between 1 and 10 in every 10,000 people are likely to get these):

- inflammation of the bowel (colitis) linked to antibiotic use (can be fatal in very rare cases) (see Section 2: Take special care with Ciprofloxacin Bayer)
- changes to the blood count (leukopenia, leukocytosis, neutropenia, anaemia), increased or decreased amounts of a blood clotting factor (thrombocytes)
- allergic reaction, swelling (oedema), or rapid swelling of the skin and mucous membranes (angio-oedema)
- increased blood sugar (hyperglycaemia)
- confusion, disorientation, anxiety reactions, strange dreams, depression, or hallucinations
- pins and needles, unusual sensitivity to stimuli of the senses, decreased skin sensitivity, tremors, seizures (see Section 2: Take special care with Ciprofloxacin Bayer), or giddiness
- eyesight problems
- tinnitus, loss of hearing, impaired hearing
- rapid heartbeat (tachycardia)
- expansion of blood vessels (vasodilation), low blood pressure, or fainting
- shortness of breath, including asthmatic symptoms
- liver disorders, jaundice (cholestatic icterus), or hepatitis
- sensitivity to light (see Section 2: Take special care with Ciprofloxacin Bayer)
- muscle pain, inflammation of the joints, increased muscle tone, or cramp
- kidney failure, blood or crystals in the urine (see Section 2: Take special care with Ciprofloxacin Bayer), urinary tract inflammation
- fluid retention or excessive sweating
- abnormal levels of a clotting factor (prothrombin) or increased levels of the enzyme amylase

Very rare side effects (less than 1 in every 10,000 people are likely to get these):

- a special type of reduced red blood cell count (haemolytic anaemia); a dangerous drop in a type of white blood cells (agranulocytosis); a drop in the number of red and white blood cells and platelets (pancytopenia), which may be fatal; and bone marrow depression, which may also be fatal (see Section 2: Take special care with Ciprofloxacin Bayer)
- severe allergic reactions (anaphylactic reaction or anaphylactic shock, which can be fatal - serum sickness) (see Section 2: Take special care with Ciprofloxacin Bayer)
- mental disturbances (psychotic reactions) (see Section 2: Take special care with Ciprofloxacin Bayer)
- migraine, disturbed coordination, unsteady walk (gait disturbance), disorder of sense of smell (olfactory disorders), pressure on the brain (intracranial pressure)
- visual colour distortions
- inflammation of the wall of the blood vessels (vasculitis)
- pancreatitis
- death of liver cells (liver necrosis) very rarely leading to life-threatening liver failure
- small, pin-point bleeding under the skin (petechiae); various skin eruptions or rashes (for example, the potentially fatal Stevens-Johnson syndrome or toxic epidermal necrolysis)
- muscle weakness, tendon inflammation, tendon rupture – especially of the large tendon at the back of the ankle (Achilles tendon) (see Section 2: Take special care with Ciprofloxacin Bayer); worsening of the symptoms of myasthenia gravis (see Section 2: Take special care with Ciprofloxacin Bayer)

Frequency not known (cannot be estimated from the available data)
- troubles associated with the nervous system such as pain, burning, tingling, numbness and/ or weakness in extremities
- severe cardiac rhythm abnormalities, irregular heart beat (Torsades de Pointes)

5. HOW TO STORE CIPROFLOXACIN BAYER

[To be completed nationally]

Keep out of the reach and sight of children.

Do not use Ciprofloxacin Bayer after the expiry date, which is stated on the carton after "EXP": The expiry date refers to the last day of the month concerned.

Medicines should not be disposed of down the drain or with household rubbish. Ask your pharmacist how to dispose of any medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ciprofloxacin Bayer contains

[To be completed nationally]

What Ciprofloxacin Bayer looks like and contents of the pack

Oral suspension (in single dose sachets)
[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

Spain: Baycip

This leaflet was last approved in {MM/YYYY}

[To be completed nationally]

Advice/medical education

Antibiotics are used to cure bacterial infections. They are ineffective against viral infections.
If your doctor has prescribed antibiotics, you need them precisely for your current illness.
Despite antibiotics, some bacteria may survive or grow. This phenomenon is called resistance: some antibiotic treatments become ineffective.
Misuse of antibiotics increases resistance. You may even help bacteria become resistant and therefore delay your cure or decrease antibiotic efficacy if you do not respect appropriate:
- dosages
- schedules
- duration of treatment

Consequently, to preserve the efficacy of this drug:
1 - Use antibiotics only when prescribed.
2 - Strictly follow the prescription.
3 - Do not re-use an antibiotic without medical prescription, even if you want to treat a similar illness.
4 - Never give your antibiotic to another person; maybe it is not adapted to her/his illness.

5 - After completion of treatment, return all unused drugs to your chemist’s shop to ensure they will be disposed of correctly

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ciprofloxacin Bayer and associated names (see Annex I) 500 mg oral suspension in single-dose sachets
[See Annex I - To be completed nationally]

Ciprofloxacin

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT CIPROFLOXACIN BAYER IS AND WHAT IT IS USED FOR

Ciprofloxacin Bayer is an antibiotic belonging to the fluoroquinolone family. The active substance is ciprofloxacin. Ciprofloxacin works by killing bacteria that cause infections. It only works with specific strains of bacteria.

Adults

Ciprofloxacin Bayer is used in adults to treat the following bacterial infections:

- respiratory tract infections
- long lasting or recurring ear or sinus infections
- urinary tract infections
- infections of the testicles
- genital organ infections in women
- gastro-intestinal tract infections and intra-abdominal infections
- skin and soft tissue infections
- bone and joint infections
- to treat infections in patients with a very low white blood cell count (neutropenia)
- to prevent infections in patients with a very low white blood cell count (neutropenia)
- to prevent infections due to the bacterium *Neisseria meningitidis*
- anthrax inhalation exposure

If you have a severe infection or one that is caused by more than one type of bacterium, you may be given additional antibiotic treatment in addition to Ciprofloxacin Bayer.

Children and adolescents

Ciprofloxacin Bayer is used in children and adolescents, under specialist medical supervision, to treat the following bacterial infections:

- lung and bronchial infections in children and adolescents suffering from cystic fibrosis
- complicated urinary tract infections, including infections that have reached the kidneys (pyelonephritis)
- anthrax inhalation exposure

Ciprofloxacin Bayer may also be used to treat other specific severe infections in children and adolescents when your doctor considered this necessary.

2. BEFORE YOU TAKE CIPROFLOXACIN BAYER

Do not take Ciprofloxacin Bayer if you are:

- allergic (hypersensitive) to the active substance, to other quinolone drugs or to any of the other ingredients of Ciprofloxacin Bayer (see section 6)
- taking tizanidine (see Section 2: Taking other medicines)

Take special care with Ciprofloxacin Bayer

Before taking Ciprofloxacin Bayer

Tell your doctor if you:

- have ever had kidney problems because your treatment may need to be adjusted
- suffer from epilepsy or other neurological conditions
- have a history of tendon problems during previous treatment with antibiotics such as Ciprofloxacin Bayer
- have myasthenia gravis (a type of muscle weakness)
- have a history of abnormal heart rhythms (arrythmias)

While taking Ciprofloxacin Bayer

Tell your doctor immediately, if any of the following occurs **while taking Ciprofloxacin Bayer**. Your doctor will decide whether treatment with Ciprofloxacin Bayer needs to be stopped.

- **Severe, sudden allergic reaction** (an anaphylactic reaction/shock, angio-oedema). Even with the first dose, there is a small chance that you may experience a severe allergic reaction with the following symptoms: tightness in the chest, feeling dizzy, sick or faint, or experiencing dizziness when standing up. **If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.**

- **Pain and swelling in the joints and tendinitis** may occur occasionally, particularly if you are elderly and are also being treated with corticosteroids. At the first sign of any pain or inflammation stop taking Ciprofloxacin Bayer and rest the painful area. Avoid any unnecessary exercise, as this might increase the risk of a tendon rupture.

- If you suffer from **epilepsy** or other **neurological conditions** such as cerebral ischemia or stroke, you may experience side effects associated with the central nervous system. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience **psychiatric reactions** the first time you take Ciprofloxacin Bayer. If you suffer from **depression** or **psychosis**, your symptoms may become worse under treatment with Ciprofloxacin Bayer. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience symptoms of neuropathy such as pain, burning, tingling, numbness and/or weakness. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- **Diarrhoea** may develop while you are taking antibiotics, including Ciprofloxacin Bayer, or even several weeks after you have stopped taking them. If it becomes severe or persistent or you notice that your stool contains blood or mucus, stop taking Ciprofloxacin Bayer immediately, as this can be life-threatening. Do not take medicines that stop or slow down bowel movements and contact your doctor.

- Tell the doctor or laboratory staff that you are taking Ciprofloxacin Bayer if you have to provide a **blood or urine sample.**

- Ciprofloxacin Bayer may cause **liver damage**. If you notice any symptoms such as loss of appetite, jaundice (yellowing of the skin), dark urine, itching, or tenderness of the stomach, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- Ciprofloxacin Bayer may cause a reduction in the number of white blood cells and your **resistance to infection may be decreased**. If you experience an infection with symptoms such as fever and serious deterioration of your general condition, or fever with local infection symptoms such as sore throat/pharynx/mouth or urinary problems you should see your doctor immediately. A blood test will be taken to check possible reduction of white blood cells (agranulocytosis). It is important to inform your doctor about your medicine.

- Tell your doctor if you or a member of your family is known to have a deficiency in glucose-6-phosphate dehydrogenase (G6PD), since you may experience a risk of anemia with ciprofloxacin.

- Your skin becomes more **sensitive to sunlight or ultraviolet (UV) light** when taking Ciprofloxacin Bayer. Avoid exposure to strong sunlight, or artificial UV light such as sunbeds.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including any that you obtained without a prescription.

Do not take Ciprofloxacin Bayer together with tizanidine, because this may cause side effects such as low blood pressure and sleepiness (see Section 2: "Do not take Ciprofloxacin Bayer").

The following medicines are known to interact with Ciprofloxacin Bayer in your body. Taking Ciprofloxacin Bayer together with these medicines can influence the therapeutic effect of those medicines. It can also increase the probability of experiencing side effects.

Tell your doctor if you are taking:

- warfarin or other oral anti-coagulants (to thin the blood)
- probenecid (for gout)
- methotrexate (for certain types of cancer, psoriasis, rheumatoid arthritis)
- theophylline (for breathing problems)
- tizanidine (for muscle spasticity in multiple sclerosis)
- clozapine (an antipsychotic)

- ropinirole (for Parkinson's disease)
- phenytoin (for epilepsy)

Ciprofloxacin Bayer may **increase** the levels of the following medicines in your blood:

- pentoxifylline (for circulatory disorders)
- caffeine

Some medicines **reduce** the effect of Ciprofloxacin Bayer. Tell your doctor if you take or wish to take:

- antacids
- mineral supplements
- sucralfate
- a polymeric phosphate binder (e.g. sevelamer)
- medicines or supplements containing calcium, magnesium, aluminium or iron

If these preparations are essential, take Ciprofloxacin Bayer about two hours before or no sooner than four hours after them.

Taking Ciprofloxacin Bayer with food and drink

Unless you take Ciprofloxacin Bayer during meals, do not eat or drink any dairy products (such as milk or yoghurt) or drinks with added calcium when you take the suspension, as they may affect the absorption of the active substance.

Pregnancy and breast-feeding

It is preferable to avoid the use of Ciprofloxacin Bayer during pregnancy. Tell your doctor if you are planning to get pregnant.

Do not take Ciprofloxacin Bayer during breast feeding because ciprofloxacin is excreted in breast milk and can be harmful for your child.

Driving and using machines

Ciprofloxacin Bayer may make you feel less alert. Some neurological adverse events can occur. Therefore, make sure you know how you react to Ciprofloxacin Bayer before driving a vehicle or operating machinery. If in doubt, talk to your doctor.

3. HOW TO TAKE CIPROFLOXACIN BAYER

Your doctor will explain to you exactly how much Ciprofloxacin Bayer you will have to take as well as how often and for how long. This will depend on the type of infection you have and how bad it is.

Tell your doctor if you suffer from kidney problems because your dose may need to be adjusted.

The treatment usually lasts from 5 to 21 days, but may take longer for severe infections. Take the suspension exactly as your doctor has told you. Ask your doctor or pharmacist if you are not sure how many sachets to take and how to take Ciprofloxacin Bayer.

Taking the suspension

Shake the sachet applying slight pressure to the walls. Then tear the sachet open as indicated and take the contents directly.

You can take the sachets at mealtimes or in between meals. Any calcium you take as part of a meal will not seriously affect uptake. However, **do not** take Ciprofloxacin Bayer suspension with dairy products such as milk or yoghurt or with fortified fruit-juice (e.g. calcium-fortified orange-juice)

Remember to drink plenty of fluids while you are taking Ciprofloxacin Bayer.

Do try to take the sachet at around the same time every day.

If you take more Ciprofloxacin Bayer than you should

- If you take more than the prescribed dose, get medical help immediately. If possible, take the sachets or the box with you to show the doctor.

If you forget to take Ciprofloxacin Bayer

- Take the normal dose as soon as possible and then continue as prescribed. However, if it is almost time for your next dose, do not take the missed dose and continue as usual. Do not take a double dose to make up for a forgotten dose. Be sure to complete your course of treatment.

If you stop taking Ciprofloxacin Bayer

- It is important that you **finish the course of treatment** even if you begin to feel better after a few days. If you stop taking this medicine too soon, your infection may not be completely cured and the symptoms of the infection may return or get worse. You might also develop resistance to the antibiotic.

If you have any more questions about the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ciprofloxacin Bayer can cause side effects, although not everybody gets them.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

Common side effects (between 1 and 10 in every 100 people are likely to get these):

- nausea, diarrhoea
- joint pains in children

Uncommon side effects (between 1 and 10 in every 1,000 people are likely to get these):

- fungal superinfections
- a high concentration of eosinophils, a type of white blood cell
- loss of appetite (anorexia)
- hyperactivity or agitation
- headache, dizziness, sleeping problems, or taste disorders
- vomiting, abdominal pain, digestive problems such as stomach upset (indigestion/heartburn), or wind
- increased amounts of certain substances in the blood (transaminases and/or bilirubin)
- rash, itching, or hives
- joint pain in adults
- poor kidney function
- pains in your muscles and bones, feeling unwell (asthenia), or fever
- increase in blood alkaline phosphatase (a certain substance in the blood)

Rare side effects (between 1 and 10 in every 10,000 people are likely to get these):

- inflammation of the bowel (colitis) linked to antibiotic use (can be fatal in very rare cases) (see Section 2: Take special care with Ciprofloxacin Bayer)
- changes to the blood count (leukopenia, leukocytosis, neutropenia, anaemia), increased or decreased amounts of a blood clotting factor (thrombocytes)
- allergic reaction, swelling (oedema), or rapid swelling of the skin and mucous membranes (angio-oedema)
- increased blood sugar (hyperglycaemia)
- confusion, disorientation, anxiety reactions, strange dreams, depression, or hallucinations
- pins and needles, unusual sensitivity to stimuli of the senses, decreased skin sensitivity, tremors, seizures (see Section 2: Take special care with Ciprofloxacin Bayer), or giddiness
- eyesight problems
- tinnitus, loss of hearing, impaired hearing
- rapid heartbeat (tachycardia)
- expansion of blood vessels (vasodilation), low blood pressure, or fainting
- shortness of breath, including asthmatic symptoms
- liver disorders, jaundice (cholestatic icterus), or hepatitis
- sensitivity to light (see Section 2: Take special care with Ciprofloxacin Bayer)
- muscle pain, inflammation of the joints, increased muscle tone, or cramp
- kidney failure, blood or crystals in the urine (see Section 2: Take special care with Ciprofloxacin Bayer), urinary tract inflammation
- fluid retention or excessive sweating
- abnormal levels of a clotting factor (prothrombin) or increased levels of the enzyme amylase

Very rare side effects (less than 1 in every 10,000 people are likely to get these):

- a special type of reduced red blood cell count (haemolytic anaemia); a dangerous drop in a type of white blood cells (agranulocytosis); a drop in the number of red and white blood cells and platelets (pancytopenia), which may be fatal; and bone marrow depression, which may also be fatal (see Section 2: Take special care with Ciprofloxacin Bayer)
- severe allergic reactions (anaphylactic reaction or anaphylactic shock, which can be fatal - serum sickness) (see Section 2: Take special care with Ciprofloxacin Bayer)
- mental disturbances (psychotic reactions) (see Section 2: Take special care with Ciprofloxacin Bayer)
- migraine, disturbed coordination, unsteady walk (gait disturbance), disorder of sense of smell (olfactory disorders), pressure on the brain (intracranial pressure)
- visual colour distortions
- inflammation of the wall of the blood vessels (vasculitis)
- pancreatitis
- death of liver cells (liver necrosis) very rarely leading to life-threatening liver failure
- small, pin-point bleeding under the skin (petechiae); various skin eruptions or rashes (for example, the potentially fatal Stevens-Johnson syndrome or toxic epidermal necrolysis)
- muscle weakness, tendon inflammation, tendon rupture – especially of the large tendon at the back of the ankle (Achilles tendon) (see Section 2: Take special care with Ciprofloxacin Bayer); worsening of the symptoms of myasthenia gravis (see Section 2: Take special care with Ciprofloxacin Bayer)

Frequency not known (cannot be estimated from the available data)
- troubles associated with the nervous system such as pain, burning, tingling, numbness and/ or weakness in extremities
- severe cardiac rhythm abnormalities, irregular heart beat (Torsades de Pointes)

5. HOW TO STORE CIPROFLOXACIN BAYER

[To be completed nationally]

Keep out of the reach and sight of children.

Do not use Ciprofloxacin Bayer after the expiry date, which is stated on the carton after "EXP": The expiry date refers to the last day of the month concerned.

Medicines should not be disposed of down the drain or with household rubbish. Ask your pharmacist how to dispose of any medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ciprofloxacin Bayer contains

[To be completed nationally]

What Ciprofloxacin Bayer looks like and contents of the pack

Oral suspension (in single dose sachets)
[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

Spain: Baycip

This leaflet was last approved in {MM/YYYY}

[To be completed nationally]

Advice/medical education

Antibiotics are used to cure bacterial infections. They are ineffective against viral infections.
If your doctor has prescribed antibiotics, you need them precisely for your current illness.
Despite antibiotics, some bacteria may survive or grow. This phenomenon is called resistance: some antibiotic treatments become ineffective.
Misuse of antibiotics increases resistance. You may even help bacteria become resistant and therefore delay your cure or decrease antibiotic efficacy if you do not respect appropriate:
- dosages
- schedules
- duration of treatment

Consequently, to preserve the efficacy of this drug:
1 - Use antibiotics only when prescribed.
2 - Strictly follow the prescription.
3 - Do not re-use an antibiotic without medical prescription, even if you want to treat a similar illness.
4 - Never give your antibiotic to another person; maybe it is not adapted to her/his illness.

5 - After completion of treatment, return all unused drugs to your chemist’s shop to ensure they will be disposed of correctly

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ciprofloxacin Bayer and associated names (see Annex I) 50 mg/mL granules and solvent for oral suspension

[See Annex I - To be completed nationally]

Ciprofloxacin

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT CIPROFLOXACIN BAYER IS AND WHAT IT IS USED FOR

Ciprofloxacin Bayer is an antibiotic belonging to the fluoroquinolone family. The active substance is ciprofloxacin. Ciprofloxacin works by killing bacteria that cause infections. It only works with specific strains of bacteria.

Adults

Ciprofloxacin Bayer is used in adults to treat the following bacterial infections:

- respiratory tract infections
- long lasting or recurring ear or sinus infections
- urinary tract infections
- infections of the testicles
- genital organ infections in women
- gastro-intestinal tract infections and intra-abdominal infections
- skin and soft tissue infections
- bone and joint infections
- to treat infections in patients with a very low white blood cell count (neutropenia)
- to prevent infections in patients with a very low white blood cell count (neutropenia)
- to prevent infections due to the bacterium *Neisseria meningitidis*
- anthrax inhalation exposure

If you have a severe infection or one that is caused by more than one type of bacterium, you may be given additional antibiotic treatment in addition to Ciprofloxacin Bayer.

Children and adolescents

Ciprofloxacin Bayer is used in children and adolescents, under specialist medical supervision, to treat the following bacterial infections:

- lung and bronchial infections in children and adolescents suffering from cystic fibrosis
- complicated urinary tract infections, including infections that have reached the kidneys (pyelonephritis)
- anthrax inhalation exposure

Ciprofloxacin Bayer may also be used to treat other specific severe infections in children and adolescents when your doctor considered this necessary.

2. BEFORE YOU TAKE CIPROFLOXACIN BAYER

Do not take Ciprofloxacin Bayer if you are:

- allergic (hypersensitive) to the active substance, to other quinolone drugs or to any of the other ingredients of Ciprofloxacin Bayer (see section 6)
- taking tizanidine (see Section 2: Taking other medicines)

Take special care with Ciprofloxacin Bayer

Before taking Ciprofloxacin Bayer

Tell your doctor if you:

- have ever had kidney problems because your treatment may need to be adjusted
- suffer from epilepsy or other neurological conditions
- have a history of tendon problems during previous treatment with antibiotics such as Ciprofloxacin Bayer
- have myasthenia gravis (a type of muscle weakness)
- have a history of abnormal heart rhythms (arrythmias)

While taking Ciprofloxacin Bayer

Tell your doctor immediately, if any of the following occurs **while taking Ciprofloxacin Bayer**. Your doctor will decide whether treatment with Ciprofloxacin Bayer needs to be stopped.

- **Severe, sudden allergic reaction** (an anaphylactic reaction/shock, angio-oedema). Even with the first dose, there is a small chance that you may experience a severe allergic reaction with the following symptoms: tightness in the chest, feeling dizzy, sick or faint, or experiencing dizziness when standing up. **If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.**

- **Pain and swelling in the joints and tendinitis** may occur occasionally, particularly if you are elderly and are also being treated with corticosteroids. At the first sign of any pain or inflammation stop taking Ciprofloxacin Bayer and rest the painful area. Avoid any unnecessary exercise, as this might increase the risk of a tendon rupture.

- If you suffer from **epilepsy** or other **neurological conditions** such as cerebral ischemia or stroke, you may experience side effects associated with the central nervous system. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience **psychiatric reactions** the first time you take Ciprofloxacin Bayer. If you suffer from **depression** or **psychosis**, your symptoms may become worse under treatment with Ciprofloxacin Bayer. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience symptoms of neuropathy such as pain, burning, tingling, numbness and/or weakness. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- **Diarrhoea** may develop while you are taking antibiotics, including Ciprofloxacin Bayer, or even several weeks after you have stopped taking them. If it becomes severe or persistent or you notice that your stool contains blood or mucus, stop taking Ciprofloxacin Bayer immediately, as this can be life-threatening. Do not take medicines that stop or slow down bowel movements and contact your doctor.

- Tell the doctor or laboratory staff that you are taking Ciprofloxacin Bayer if you have to provide a **blood or urine sample**.

- Ciprofloxacin Bayer may cause **liver damage**. If you notice any symptoms such as loss of appetite, jaundice (yellowing of the skin), dark urine, itching, or tenderness of the stomach, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- Ciprofloxacin Bayer may cause a reduction in the number of white blood cells and your **resistance to infection may be decreased**. If you experience an infection with symptoms such as fever and serious deterioration of your general condition, or fever with local infection symptoms such as sore throat/pharynx/mouth or urinary problems you should see your doctor immediately. A blood test will be taken to check possible reduction of white blood cells (agranulocytosis). It is important to inform your doctor about your medicine.

- Tell your doctor if you or a member of your family is known to have a deficiency in glucose-6-phosphate dehydrogenase (G6PD), since you may experience a risk of anemia with ciprofloxacin.

- Your skin becomes more **sensitive to sunlight or ultraviolet (UV) light** when taking Ciprofloxacin Bayer. Avoid exposure to strong sunlight, or artificial UV light such as sunbeds.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including any that you obtained without a prescription.

Do not take Ciprofloxacin Bayer together with tizanidine, because this may cause side effects such as low blood pressure and sleepiness (see Section 2: "Do not take Ciprofloxacin Bayer").

The following medicines are known to interact with Ciprofloxacin Bayer in your body. Taking Ciprofloxacin Bayer together with these medicines can influence the therapeutic effect of those medicines. It can also increase the probability of experiencing side effects.

Tell your doctor if you are taking:

- warfarin or other oral anti-coagulants (to thin the blood)
- probenecid (for gout)
- methotrexate (for certain types of cancer, psoriasis, rheumatoid arthritis)
- theophylline (for breathing problems)
- tizanidine (for muscle spasticity in multiple sclerosis)
- clozapine (an antipsychotic)

- ropinirole (for Parkinson's disease)
- phenytoin (for epilepsy)

Ciprofloxacin Bayer may **increase** the levels of the following medicines in your blood:

- pentoxifylline (for circulatory disorders)
- caffeine

Some medicines **reduce** the effect of Ciprofloxacin Bayer. Tell your doctor if you take or wish to take:

- antacids
- mineral supplements
- sucralfate
- a polymeric phosphate binder (e.g. sevelamer)
- medicines or supplements containing calcium, magnesium, aluminium or iron

If these preparations are essential, take Ciprofloxacin Bayer about two hours before or no sooner than four hours after them.

Taking Ciprofloxacin Bayer with food and drink

Unless you take Ciprofloxacin Bayer during meals, do not eat or drink any dairy products (such as milk or yoghurt) or drinks with added calcium when you take the suspension, as they may affect the absorption of the active substance.

Pregnancy and breast-feeding

It is preferable to avoid the use of Ciprofloxacin Bayer during pregnancy. Tell your doctor if you are planning to get pregnant.

Do not take Ciprofloxacin Bayer during breast feeding because ciprofloxacin is excreted in breast milk and can be harmful for your child.

Driving and using machines

Ciprofloxacin Bayer may make you feel less alert. Some neurological adverse events can occur. Therefore, make sure you know how you react to Ciprofloxacin Bayer before driving a vehicle or operating machinery. If in doubt, talk to your doctor.

Important information about some of the ingredients of Ciprofloxacin Bayer

As Ciprofloxacin Bayer contains 1.4 g sucrose per 5-mL measuring spoonful, this has to be taken into consideration in terms of daily intake.

3. HOW TO TAKE CIPROFLOXACIN BAYER

Your doctor will explain to you exactly how much Ciprofloxacin Bayer you will have to take as well as how often and for how long. This will depend on the type of infection you have and how bad it is.

Tell your doctor if you suffer from kidney problems because your dose may need to be adjusted.

The treatment usually lasts from 5 to 21 days, but may take longer for severe infections. Take the suspension exactly as your doctor has told you. Ask your doctor or pharmacist if you are not sure how to take Ciprofloxacin Bayer.

Preparing and taking the suspension

The product comes in 2 bottles. The small bottle contains granules which you add to the solvent in the larger bottle.

1. Open both bottles. Press down the child-proof cap and turn it to the left.
2. Empty the bottle containing the granules for oral suspension into the opening of the bottle of solvent. Do not add any water to the solvent.
3. Close the bottle with the solvent and added granules, turn it on its side and shake vigorously for about 15 seconds.
4. Shake it vigorously for about 15 seconds before each dose. The reconstituted suspension is stable for no more than about 14 days even when stored in a refrigerator.
5. Do try to take the suspension at around the same time every day.
6. Always use the measuring spoon provided. The full spoon will give you a dose of 250 mg Ciprofloxacin Bayer.
7. A glass of water may be taken after taking the dose.
8. You can take the suspension at mealtimes or in between meals. Any calcium you take as part of a meal will not seriously affect uptake. However, **do not** take Ciprofloxacin Bayer suspension with dairy products such as milk or yoghurt or with fortified fruit-juice (e.g. calcium-fortified orange-juice).

Remember to drink plenty of fluids while you are taking Ciprofloxacin Bayer.

If you take more Ciprofloxacin Bayer than you should

- If you take more than the prescribed dose, get medical help immediately. If possible, take the oral suspension or the box with you to show the doctor.

If you forget to take Ciprofloxacin Bayer

- Take the normal dose as soon as possible and then continue as prescribed. However, if it is almost time for your next dose, do not take the missed dose and continue as usual. Do not take a double dose to make up for a forgotten dose. Be sure to complete your course of treatment.

If you stop taking Ciprofloxacin Bayer

- It is important that you **finish the course of treatment** even if you begin to feel better after a few days. If you stop taking this medicine too soon, your infection may not be completely cured and the symptoms of the infection may return or get worse. You might also develop resistance to the antibiotic.

If you have any more questions about the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ciprofloxacin Bayer can cause side effects, although not everybody gets them.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

Common side effects (between 1 and 10 in every 100 people are likely to get these):

- nausea, diarrhoea
- joint pains in children

Uncommon side effects (between 1 and 10 in every 1,000 people are likely to get these):

- fungal superinfections
- a high concentration of eosinophils, a type of white blood cell
- loss of appetite (anorexia)
- hyperactivity or agitation
- headache, dizziness, sleeping problems, or taste disorders
- vomiting, abdominal pain, digestive problems such as stomach upset (indigestion/heartburn), or wind
- increased amounts of certain substances in the blood (transaminases and/or bilirubin)
- rash, itching, or hives
- joint pain in adults
- poor kidney function
- pains in your muscles and bones, feeling unwell (asthenia), or fever
- increase in blood alkaline phosphatase (a certain substance in the blood)

Rare side effects (between 1 and 10 in every 10,000 people are likely to get these):

- inflammation of the bowel (colitis) linked to antibiotic use (can be fatal in very rare cases) (see Section 2: Take special care with Ciprofloxacin Bayer)
- changes to the blood count (leukopenia, leukocytosis, neutropenia, anaemia), increased or decreased amounts of a blood clotting factor (thrombocytes)
- allergic reaction, swelling (oedema), or rapid swelling of the skin and mucous membranes (angio-oedema)
- increased blood sugar (hyperglycaemia)
- confusion, disorientation, anxiety reactions, strange dreams, depression, or hallucinations
- pins and needles, unusual sensitivity to stimuli of the senses, decreased skin sensitivity, tremors, seizures (see Section 2: Take special care with Ciprofloxacin Bayer), or giddiness
- eyesight problems
- tinnitus, loss of hearing, impaired hearing
- rapid heartbeat (tachycardia)
- expansion of blood vessels (vasodilation), low blood pressure, or fainting
- shortness of breath, including asthmatic symptoms
- liver disorders, jaundice (cholestatic icterus), or hepatitis
- sensitivity to light (see Section 2: Take special care with Ciprofloxacin Bayer)
- muscle pain, inflammation of the joints, increased muscle tone, or cramp
- kidney failure, blood or crystals in the urine (see Section 2: Take special care with Ciprofloxacin Bayer), urinary tract inflammation
- fluid retention or excessive sweating
- abnormal levels of a clotting factor (prothrombin) or increased levels of the enzyme amylase

Very rare side effects (less than 1 in every 10,000 people are likely to get these):

- a special type of reduced red blood cell count (haemolytic anaemia); a dangerous drop in a type of white blood cells (agranulocytosis); a drop in the number of red and white blood cells and platelets (pancytopenia), which may be fatal; and bone marrow depression, which may also be fatal (see Section 2: Take special care with Ciprofloxacin Bayer)
- severe allergic reactions (anaphylactic reaction or anaphylactic shock, which can be fatal - serum sickness) (see Section 2: Take special care with Ciprofloxacin Bayer)
- mental disturbances (psychotic reactions) (see Section 2: Take special care with Ciprofloxacin Bayer)
- migraine, disturbed coordination, unsteady walk (gait disturbance), disorder of sense of smell (olfactory disorders), pressure on the brain (intracranial pressure)
- visual colour distortions
- inflammation of the wall of the blood vessels (vasculitis)
- pancreatitis
- death of liver cells (liver necrosis) very rarely leading to life-threatening liver failure

- small, pin-point bleeding under the skin (petechiae); various skin eruptions or rashes (for example, the potentially fatal Stevens-Johnson syndrome or toxic epidermal necrolysis)
- muscle weakness, tendon inflammation, tendon rupture – especially of the large tendon at the back of the ankle (Achilles tendon) (see Section 2: Take special care with Ciprofloxacin Bayer); worsening of the symptoms of myasthenia gravis (see Section 2: Take special care with Ciprofloxacin Bayer)

Frequency not known (cannot be estimated from the available data)
- troubles associated with the nervous system such as pain, burning, tingling, numbness and/ or weakness in extremities
- severe cardiac rhythm abnormalities, irregular heart beat (Torsades de Pointes)

5. HOW TO STORE CIPROFLOXACIN BAYER

[To be completed nationally]

Keep out of the reach and sight of children.

Do not use Ciprofloxacin Bayer after the expiry date, which is stated on the carton after "EXP": The expiry date refers to the last day of the month concerned.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ciprofloxacin Bayer contains

[To be completed nationally]

What Ciprofloxacin Bayer looks like and contents of the pack

Granules and solvent for oral suspension
[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria:	Ciproxin
Belgium:	Ciproxine
Denmark:	Ciproxin
France:	Ciflox
Germany:	Ciprobay
Greece:	Ciproxin
Ireland:	Ciproxin

Italy:	Ciproxin
Luxembourg:	Ciproxine
Netherlands:	Ciproxin
Portugal:	Ciproxina
Romania:	Ciproxin
Sweden:	Ciproxin
United Kingdom:	Ciproxin

This leaflet was last approved in {MM/YYYY}

[To be completed nationally]

Advice/medical education

Antibiotics are used to cure bacterial infections. They are ineffective against viral infections.
If your doctor has prescribed antibiotics, you need them precisely for your current illness.
Despite antibiotics, some bacteria may survive or grow. This phenomenon is called resistance: some antibiotic treatments become ineffective.
Misuse of antibiotics increases resistance. You may even help bacteria become resistant and therefore delay your cure or decrease antibiotic efficacy if you do not respect appropriate:

- dosages
- schedules
- duration of treatment

Consequently, to preserve the efficacy of this drug:

1 - Use antibiotics only when prescribed.
2 - Strictly follow the prescription.
3 - Do not re-use an antibiotic without medical prescription, even if you want to treat a similar illness.
4 - Never give your antibiotic to another person; maybe it is not adapted to her/his illness.
5 - After completion of treatment, return all unused drugs to your chemist's shop to ensure they will be disposed of correctly

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ciprofloxacin Bayer and associated names (see Annex I) 100 mg/mL granules and solvent for oral suspension
[See Annex I - To be completed nationally]

Ciprofloxacin

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT CIPROFLOXACIN BAYER IS AND WHAT IT IS USED FOR

Ciprofloxacin Bayer is an antibiotic belonging to the fluoroquinolone family. The active substance is ciprofloxacin. Ciprofloxacin works by killing bacteria that cause infections. It only works with specific strains of bacteria.

Adults

Ciprofloxacin Bayer is used in adults to treat the following bacterial infections:

- respiratory tract infections
- long lasting or recurring ear or sinus infections
- urinary tract infections
- infections of the testicles
- genital organ infections in women
- gastro-intestinal tract infections and intra-abdominal infections
- skin and soft tissue infections
- bone and joint infections
- to treat infections in patients with a very low white blood cell count (neutropenia)
- to prevent infections in patients with a very low white blood cell count (neutropenia)
- to prevent infections due to the bacterium *Neisseria meningitidis*
- anthrax inhalation exposure

If you have a severe infection or one that is caused by more than one type of bacterium, you may be given additional antibiotic treatment in addition to Ciprofloxacin Bayer.

Children and adolescents

Ciprofloxacin Bayer is used in children and adolescents, under specialist medical supervision, to treat the following bacterial infections:

- lung and bronchial infections in children and adolescents suffering from cystic fibrosis
- complicated urinary tract infections, including infections that have reached the kidneys (pyelonephritis)
- anthrax inhalation exposure

Ciprofloxacin Bayer may also be used to treat other specific severe infections in children and adolescents when your doctor considered this necessary.

2. BEFORE YOU TAKE CIPROFLOXACIN BAYER

Do not take Ciprofloxacin Bayer if you are:

- allergic (hypersensitive) to the active substance, to other quinolone drugs or to any of the other ingredients of Ciprofloxacin Bayer (see section 6)
- taking tizanidine (see Section 2: Taking other medicines)

Take special care with Ciprofloxacin Bayer

Before taking Ciprofloxacin Bayer

Tell your doctor if you:

- have ever had kidney problems because your treatment may need to be adjusted
- suffer from epilepsy or other neurological conditions
- have a history of tendon problems during previous treatment with antibiotics such as Ciprofloxacin Bayer
- have myasthenia gravis (a type of muscle weakness)
- have a history of abnormal heart rhythms (arrythmias)

While taking Ciprofloxacin Bayer

Tell your doctor immediately, if any of the following occurs **while taking Ciprofloxacin Bayer**. Your doctor will decide whether treatment with Ciprofloxacin Bayer needs to be stopped.

- **Severe, sudden allergic reaction** (an anaphylactic reaction/shock, angio-oedema). Even with the first dose, there is a small chance that you may experience a severe allergic reaction with the following symptoms: tightness in the chest, feeling dizzy, sick or faint, or experiencing dizziness when standing up. **If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.**

- **Pain and swelling in the joints and tendinitis** may occur occasionally, particularly if you are elderly and are also being treated with corticosteroids. At the first sign of any pain or inflammation stop taking Ciprofloxacin Bayer and rest the painful area. Avoid any unnecessary exercise, as this might increase the risk of a tendon rupture.

- If you suffer from **epilepsy** or other **neurological conditions** such as cerebral ischemia or stroke, you may experience side effects associated with the central nervous system. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience **psychiatric reactions** the first time you take Ciprofloxacin Bayer. If you suffer from **depression** or **psychosis**, your symptoms may become worse under treatment with Ciprofloxacin Bayer. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience symptoms of neuropathy such as pain, burning, tingling, numbness and/or weakness. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- **Diarrhoea** may develop while you are taking antibiotics, including Ciprofloxacin Bayer, or even several weeks after you have stopped taking them. If it becomes severe or persistent or you notice that your stool contains blood or mucus, stop taking Ciprofloxacin Bayer immediately, as this can be life-threatening. Do not take medicines that stop or slow down bowel movements and contact your doctor.

- Tell the doctor or laboratory staff that you are taking Ciprofloxacin Bayer if you have to provide a **blood or urine sample**.

- Ciprofloxacin Bayer may cause **liver damage**. If you notice any symptoms such as loss of appetite, jaundice (yellowing of the skin), dark urine, itching, or tenderness of the stomach, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- Ciprofloxacin Bayer may cause a reduction in the number of white blood cells and your **resistance to infection may be decreased**. If you experience an infection with symptoms such as fever and serious deterioration of your general condition, or fever with local infection symptoms such as sore throat/pharynx/mouth or urinary problems you should see your doctor immediately. A blood test will be taken to check possible reduction of white blood cells (agranulocytosis). It is important to inform your doctor about your medicine.

- Tell your doctor if you or a member of your family is known to have a deficiency in glucose-6-phosphate dehydrogenase (G6PD), since you may experience a risk of anemia with ciprofloxacin.

- Your skin becomes more **sensitive to sunlight or ultraviolet (UV) light** when taking Ciprofloxacin Bayer. Avoid exposure to strong sunlight, or artificial UV light such as sunbeds.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including any that you obtained without a prescription.

Do not take Ciprofloxacin Bayer together with tizanidine, because this may cause side effects such as low blood pressure and sleepiness (see Section 2: "Do not take Ciprofloxacin Bayer").

The following medicines are known to interact with Ciprofloxacin Bayer in your body. Taking Ciprofloxacin Bayer together with these medicines can influence the therapeutic effect of those medicines. It can also increase the probability of experiencing side effects.

Tell your doctor if you are taking:

- warfarin or other oral anti-coagulants (to thin the blood)
- probenecid (for gout)
- methotrexate (for certain types of cancer, psoriasis, rheumatoid arthritis)
- theophylline (for breathing problems)
- tizanidine (for muscle spasticity in multiple sclerosis)
- clozapine (an antipsychotic)

- ropinirole (for Parkinson's disease)
- phenytoin (for epilepsy)

Ciprofloxacin Bayer may **increase** the levels of the following medicines in your blood:

- pentoxifylline (for circulatory disorders)
- caffeine

Some medicines **reduce** the effect of Ciprofloxacin Bayer. Tell your doctor if you take or wish to take:

- antacids
- mineral supplements
- sucralfate
- a polymeric phosphate binder (e.g. sevelamer)
- medicines or supplements containing calcium, magnesium, aluminium or iron

If these preparations are essential, take Ciprofloxacin Bayer about two hours before or no sooner than four hours after them.

Taking Ciprofloxacin Bayer with food and drink

Unless you take Ciprofloxacin Bayer during meals, do not eat or drink any dairy products (such as milk or yoghurt) or drinks with added calcium when you take the suspension, as they may affect the absorption of the active substance.

Pregnancy and breast-feeding

It is preferable to avoid the use of Ciprofloxacin Bayer during pregnancy. Tell your doctor if you are planning to get pregnant.

Do not take Ciprofloxacin Bayer during breast feeding because ciprofloxacin is excreted in breast milk and can be harmful for your child.

Driving and using machines

Ciprofloxacin Bayer may make you feel less alert. Some neurological adverse events can occur. Therefore, make sure you know how you react to Ciprofloxacin Bayer before driving a vehicle or operating machinery. If in doubt, talk to your doctor.

Important information about some of the ingredients of Ciprofloxacin Bayer

As Ciprofloxacin Bayer contains 1.3 g sucrose per 5-mL measuring spoonful, this has to be taken into consideration in terms of daily intake.

3. HOW TO TAKE CIPROFLOXACIN BAYER

Your doctor will explain to you exactly how much Ciprofloxacin Bayer you will have to take as well as how often and for how long. This will depend on the type of infection you have and how bad it is.

Tell your doctor if you suffer from kidney problems because your dose may need to be adjusted.

The treatment usually lasts from 5 to 21 days, but may take longer for severe infections. Take the suspension exactly as your doctor has told you. Ask your doctor or pharmacist if you are not sure how to take Ciprofloxacin Bayer.

Preparing and taking the suspension

The product comes in 2 bottles. The small bottle contains granules which you add to the solvent in the larger bottle.

1. Open both bottles. Press down the child-proof cap and turn it to the left.
2. Empty the bottle containing the granules for oral suspension into the opening of the bottle of solvent. Do not add any water to the solvent.
3. Close the bottle with the solvent and added granules, turn it on its side and shake vigorously for about 15 seconds.
4. Shake it vigorously for about 15 seconds before each dose. The reconstituted suspension is stable for no more than about 14 days even when stored in a refrigerator.
5. Do try to take the suspension at around the same time every day.
6. Always use the measuring spoon provided. The full spoon will give you a dose of 500 mg Ciprofloxacin Bayer.
7. A glass of water may be taken after taking the dose.
8. You can take the suspension at mealtimes or in between meals. Any calcium you take as part of a meal will not seriously affect uptake. However, **do not** take Ciprofloxacin Bayer suspension with dairy products such as milk or yoghurt or with fortified fruit-juice (e.g. calcium-fortified orange-juice).

Remember to drink plenty of fluids while you are taking Ciprofloxacin Bayer.

If you take more Ciprofloxacin Bayer than you should

- If you take more than the prescribed dose, get medical help immediately. If possible, take the oral suspension or the box with you to show the doctor.

If you forget to take Ciprofloxacin Bayer

- Take the normal dose as soon as possible and then continue as prescribed. However, if it is almost time for your next dose, do not take the missed dose and continue as usual. Do not take a double dose to make up for a forgotten dose. Be sure to complete your course of treatment.

If you stop taking Ciprofloxacin Bayer

- It is important that you **finish the course of treatment** even if you begin to feel better after a few days. If you stop taking this medicine too soon, your infection may not be completely cured and the symptoms of the infection may return or get worse. You might also develop resistance to the antibiotic.

If you have any more questions about the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ciprofloxacin Bayer can cause side effects, although not everybody gets them.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

Common side effects (between 1 and 10 in every 100 people are likely to get these):

- nausea, diarrhoea
- joint pains in children

Uncommon side effects (between 1 and 10 in every 1,000 people are likely to get these):

- fungal superinfections
- a high concentration of eosinophils, a type of white blood cell
- loss of appetite (anorexia)
- hyperactivity or agitation
- headache, dizziness, sleeping problems, or taste disorders
- vomiting, abdominal pain, digestive problems such as stomach upset (indigestion/heartburn), or wind
- increased amounts of certain substances in the blood (transaminases and/or bilirubin)
- rash, itching, or hives
- joint pain in adults
- poor kidney function
- pains in your muscles and bones, feeling unwell (asthenia), or fever
- increase in blood alkaline phosphatase (a certain substance in the blood)

Rare side effects (between 1 and 10 in every 10,000 people are likely to get these):

- inflammation of the bowel (colitis) linked to antibiotic use (can be fatal in very rare cases) (see Section 2: Take special care with Ciprofloxacin Bayer)
- changes to the blood count (leukopenia, leukocytosis, neutropenia, anaemia), increased or decreased amounts of a blood clotting factor (thrombocytes)
- allergic reaction, swelling (oedema), or rapid swelling of the skin and mucous membranes (angio-oedema)
- increased blood sugar (hyperglycaemia)
- confusion, disorientation, anxiety reactions, strange dreams, depression, or hallucinations
- pins and needles, unusual sensitivity to stimuli of the senses, decreased skin sensitivity, tremors, seizures (see Section 2: Take special care with Ciprofloxacin Bayer), or giddiness
- eyesight problems
- tinnitus, loss of hearing, impaired hearing
- rapid heartbeat (tachycardia)
- expansion of blood vessels (vasodilation), low blood pressure, or fainting
- shortness of breath, including asthmatic symptoms
- liver disorders, jaundice (cholestatic icterus), or hepatitis
- sensitivity to light (see Section 2: Take special care with Ciprofloxacin Bayer)
- muscle pain, inflammation of the joints, increased muscle tone, or cramp
- kidney failure, blood or crystals in the urine (see Section 2: Take special care with Ciprofloxacin Bayer), urinary tract inflammation
- fluid retention or excessive sweating
- abnormal levels of a clotting factor (prothrombin) or increased levels of the enzyme amylase

Very rare side effects (less than 1 in every 10,000 people are likely to get these):

- a special type of reduced red blood cell count (haemolytic anaemia); a dangerous drop in a type of white blood cells (agranulocytosis); a drop in the number of red and white blood cells and platelets (pancytopenia), which may be fatal; and bone marrow depression, which may also be fatal (see Section 2: Take special care with Ciprofloxacin Bayer)
- severe allergic reactions (anaphylactic reaction or anaphylactic shock, which can be fatal - serum sickness) (see Section 2: Take special care with Ciprofloxacin Bayer)
- mental disturbances (psychotic reactions) (see Section 2: Take special care with Ciprofloxacin Bayer)
- migraine, disturbed coordination, unsteady walk (gait disturbance), disorder of sense of smell (olfactory disorders), pressure on the brain (intracranial pressure)
- visual colour distortions
- inflammation of the wall of the blood vessels (vasculitis)
- pancreatitis
- death of liver cells (liver necrosis) very rarely leading to life-threatening liver failure

- small, pin-point bleeding under the skin (petechiae); various skin eruptions or rashes (for example, the potentially fatal Stevens-Johnson syndrome or toxic epidermal necrolysis)
- muscle weakness, tendon inflammation, tendon rupture – especially of the large tendon at the back of the ankle (Achilles tendon) (see Section 2: Take special care with Ciprofloxacin Bayer); worsening of the symptoms of myasthenia gravis (see Section 2: Take special care with Ciprofloxacin Bayer)

Frequency not known (cannot be estimated from the available data)
- troubles associated with the nervous system such as pain, burning, tingling, numbness and/ or weakness in extremities
- severe cardiac rhythm abnormalities, irregular heart beat (Torsades de Pointes)

5. HOW TO STORE CIPROFLOXACIN BAYER

[To be completed nationally]

Keep out of the reach and sight of children.

Do not use Ciprofloxacin Bayer after the expiry date, which is stated on the carton after "EXP": The expiry date refers to the last day of the month concerned.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ciprofloxacin Bayer contains

[To be completed nationally]

What Ciprofloxacin Bayer looks like and contents of the pack

Granules and solvent for oral suspension
[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria:	Ciproxin
Denmark:	Ciproxin
France:	Ciflox
Germany:	Ciprobay
Greece:	Ciproxin
Ireland:	Ciproxin
Italy:	Ciproxin

Netherlands:	Ciproxin
Portugal:	Ciproxina
Romania:	Ciproxin
Spain:	Baycip
Sweden:	Ciproxin
United Kingdom:	Ciproxin

This leaflet was last approved in {MM/YYYY}

[To be completed nationally]

Advice/medical education

Antibiotics are used to cure bacterial infections. They are ineffective against viral infections.
If your doctor has prescribed antibiotics, you need them precisely for your current illness.
Despite antibiotics, some bacteria may survive or grow. This phenomenon is called resistance: some antibiotic treatments become ineffective.
Misuse of antibiotics increases resistance. You may even help bacteria become resistant and therefore delay your cure or decrease antibiotic efficacy if you do not respect appropriate:

- dosages
- schedules
- duration of treatment

Consequently, to preserve the efficacy of this drug:

1 - Use antibiotics only when prescribed.
2 - Strictly follow the prescription.
3 - Do not re-use an antibiotic without medical prescription, even if you want to treat a similar illness.
4 - Never give your antibiotic to another person; maybe it is not adapted to her/his illness.
5 - After completion of treatment, return all unused drugs to your chemist's shop to ensure they will be disposed of correctly

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ciprofloxacin Bayer and associated names (see Annex I) 200 mg / 100 mL solution for infusion
[See Annex I - To be completed nationally]

Ciprofloxacin

Read all of this leaflet carefully before you are given this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT CIPROFLOXACIN BAYER IS AND WHAT IT IS USED FOR

Ciprofloxacin Bayer is an antibiotic belonging to the fluoroquinolone family. The active substance is ciprofloxacin. Ciprofloxacin works by killing bacteria that cause infections. It only works with specific strains of bacteria.

Adults

Ciprofloxacin Bayer is used in adults to treat the following bacterial infections:

- respiratory tract infections
- long lasting or recurring ear or sinus infections
- urinary tract infections
- infections of the testicles
- genital organ infections in women
- gastro-intestinal tract infections and intra-abdominal infections
- skin and soft tissue infections
- bone and joint infections
- to treat infections in patients with a very low white blood cell count (neutropenia)
- to prevent infections in patients with a very low white blood cell count (neutropenia)
- anthrax inhalation exposure

If you have a severe infection or one that is caused by more than one type of bacterium, you may be given additional antibiotic treatment in addition to Ciprofloxacin Bayer.

Children and adolescents

Ciprofloxacin Bayer is used in children and adolescents, under specialist medical supervision, to treat the following bacterial infections:

- lung and bronchial infections in children and adolescents suffering from cystic fibrosis
- complicated urinary tract infections, including infections that have reached the kidneys (pyelonephritis)
- anthrax inhalation exposure

Ciprofloxacin Bayer may also be used to treat other specific severe infections in children and adolescents when your doctor considered this necessary.

2. BEFORE YOU ARE GIVEN CIPROFLOXACIN BAYER

You must not be given Ciprofloxacin Bayer if you are:

- allergic (hypersensitive) to the active substance, to other quinolone drugs or to any of the other ingredients of Ciprofloxacin Bayer (see section 6)
- taking tizanidine (see Section 2: Taking other medicines)

Take special care with Ciprofloxacin Bayer

Before you are given Ciprofloxacin Bayer

Tell your doctor if you:

- have ever had kidney problems because your treatment may need to be adjusted
- suffer from epilepsy or other neurological conditions
- have a history of tendon problems during previous treatment with antibiotics such as Ciprofloxacin Bayer
- have myasthenia gravis (a type of muscle weakness)
- have a history of abnormal heart rhythms (arrythmias)

While under treatment with Ciprofloxacin Bayer

Tell your doctor immediately, if any of the following occurs **during treatment with Ciprofloxacin Bayer**. Your doctor will decide whether treatment with Ciprofloxacin Bayer needs to be stopped.

- **Severe, sudden allergic reaction** (an anaphylactic reaction/shock, angio-oedema). Even with the first dose, there is a rare chance that you may experience a severe allergic reaction with the following symptoms: tightness in the chest, feeling dizzy, feeling sick or faint, or experience dizziness on standing. **If this happens, tell your doctor immediately since the administration of Ciprofloxacin Bayer will have to be stopped.**

- **Pain and swelling in the joints, and tendinitis** may occur occasionally, particularly if you are elderly and are also being treated with corticosteroids. At the first sign of any pain or inflammation Ciprofloxacin Bayer will have to be stopped, rest the painful area. Avoid any unnecessary exercise as this might increase the risk of a tendon rupture.

- If you suffer from **epilepsy** or other **neurological conditions** such as cerebral ischemia or stroke, you may experience side effects associated with the central nervous system. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience **psychiatric reactions** after first administration of ciprofloxacin. If you suffer from **depression** or **psychosis**, your symptoms may become worse under treatment with Ciprofloxacin Bayer. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience symptoms of neuropathy such as pain, burning, tingling, numbness and/or weakness. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- **Diarrhoea** may develop while you are on antibiotics, including Ciprofloxacin Bayer, or even several weeks after you have stopped using them. If it becomes severe or persistent or you notice that your stool contains blood or mucus tell your doctor immediately. Ciprofloxacin Bayer treatment will have to be stopped immediately, as this can be life-threatening. Do not take medicines that stop or slow down bowel movements.

- Tell the doctor or laboratory staff that you are taking Ciprofloxacin Bayer if you have to provide a **blood or urine sample**.

- Ciprofloxacin Bayer may cause **liver damage**. If you notice any symptoms such as loss of appetite, jaundice (yellowing of the skin), dark urine, itching, or tenderness of the stomach, Ciprofloxacin Bayer must be stopped immediately.

- Ciprofloxacin Bayer may cause a reduction in the number of white blood cells and your **resistance to infection may be decreased**. If you experience an infection with symptoms such as fever and serious deterioration of your general condition, or fever with local infection symptoms such as sore throat/pharynx/mouth or urinary problems you should see your doctor immediately. A blood test will be taken to check possible reduction of white blood cells (agranulocytosis). It is important to inform your doctor about your medicine.

- Tell your doctor if you or a member of your family is known to have a deficiency in glucose-6-phosphate dehydrogenase (G6PD), since you may experience a risk of anemia with ciprofloxacin.

- Your skin becomes more **sensitive to sunlight or ultraviolet (UV) light** under treatment with Ciprofloxacin Bayer. Avoid exposure to strong sunlight or artificial UV light such as sunbeds.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Do not use Ciprofloxacin Bayer together with tizanidine, because this may cause side effects such as low blood pressure and sleepiness (see Section 2: "**You must not be given Ciprofloxacin Bayer if you are**").

The following medicines are known to interact with Ciprofloxacin Bayer in your body. Using Ciprofloxacin Bayer together with these medicines can influence the therapeutic effect of these medicines. It can also increase the probability of experiencing side effects.

Tell your doctor if you are taking:

- warfarin or other oral anti-coagulants (to thin the blood)
- probenecid (for gout)
- methotrexate (for certain types of cancer, psoriasis, rheumatoid arthritis)
- theophylline (for breathing problems)
- tizanidine (for muscle spasticity in multiple sclerosis)
- clozapine (an antipsychotic)
- ropinirole (for Parkinson's disease)
- phenytoin (for epilepsy)

Ciprofloxacin Bayer may **increase** the levels of the following medicines in your blood:

- pentoxifylline (for circulatory disorders)
- caffeine

Taking Ciprofloxacin Bayer with food and drink

Food and drink does not affect your treatment with Ciprofloxacin Bayer.

Pregnancy and breast-feeding

It is preferable to avoid the use of Ciprofloxacin Bayer during pregnancy. Tell your doctor if you are planning to get pregnant.

Do not take Ciprofloxacin Bayer during breast feeding because ciprofloxacin is excreted in breast milk and can be harmful for your child.

Driving and using machines

Ciprofloxacin Bayer may make you feel less alert. Some neurological adverse events can occur. Therefore, make sure you know how you react to Ciprofloxacin Bayer before driving a vehicle or operating machinery. If in doubt, talk to your doctor.

Important information about some of the ingredients of Ciprofloxacin Bayer
Glucose
[To be completed nationally]

3. HOW TO USE CIPROFLOXACIN BAYER

Your doctor will explain to you exactly how much Ciprofloxacin Bayer you will be given as well as how often and for how long. This will depend on the type of infection you have and how bad it is.

Tell your doctor if you suffer from kidney problems because your dose may need to be adjusted.

Treatment usually lasts between 5 and 21 days, but may be longer for severe infections.

Your doctor will give you each dose by slow infusion through a vein into your bloodstream. For children, the infusion duration is 60 minutes. In adult patients, infusion time is 60 minutes for 400 mg Ciprofloxacin Bayer and 30 minutes for 200 mg Ciprofloxacin Bayer. Administering the infusion slowly helps prevent immediate side effects occurring.

Remember to drink plenty of fluids while you are taking Ciprofloxacin Bayer.

If you stop your course of Ciprofloxacin Bayer

- It is important that you **finish the course of treatment** even if you begin to feel better after a few days. If you stop using this medicine too soon your infection may not be completely cured and the symptoms of the infection may return or get worse. You might also develop resistance to the antibiotic.

If you have any more questions about the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ciprofloxacin Bayer can cause side effects, although not everybody gets them.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

Common side effects (between 1 and 10 in every 100 people are likely to get these):

- nausea, diarrhoea, vomiting
- joint pains in children
- local reaction at the injection site, rash
- temporary increased amounts of substances in the blood (transaminases)

Uncommon side effects (between 1 and 10 in every 1,000 people are likely to get these):

- fungal superinfections
- a high concentration of eosinophils, a type of white blood cell, increased or decreased amounts of a blood cloting factor (thrombocytes)
- loss of appetite (anorexia)
- hyperactivity, agitation, confusion, disorientation, hallucinations
- headache, dizziness, sleeping problems, taste disorders, pins and needles, unusual sensitivity to stimuli of the senses, seizures (see Section 2: Take special care with Ciprofloxacin Bayer), giddiness
- eyesight problems
- loss of hearing
- rapid heartbeat (tachycardia)
- expansion of the blood vessels (vasodilation), low blood pressure
- abdominal pain, digestive problems such as stomach upset (indigestion/heartburn), wind
- liver disorders, increased amounts of one substance in the blood (bilirubin), jaundice (cholestatic icterus)
- itching, hives
- joint pain in adults
- poor kidney function, kidney failure
- pains in your muscles and bones, feeling unwell (asthenia), fever, fluid retention
- increase in blood alkaline phosphatase (a certain substance in the blood)

Rare side effects (between 1 and 10 in every 10,000 people are likely to get these):

- inflammation of the bowel (colitis) linked to antibiotic use (can be fatal in rare cases) (see Section 2: Take special care with Ciprofloxacin Bayer)
- changes to the blood count (leukopenia, leukocytosis, neutropenia, anaemia), a drop in the number of red and white blood cells and platelets (pancytopenia), which may be fatal, bone-marrow depression which may also be fatal (see Section 2: Take special care with Ciprofloxacin Bayer)
- allergic reaction, allergic swelling (oedema), rapid swelling of the skin and mucous membranes (angiooedema), severe allergic reaction (anaphylactic shock) which can be life-threatening (see Section 2: Take special care with Ciprofloxacin Bayer)
- increased blood sugar (hyperglycemia)
- anxiety reaction, strange dreams, depression, mental disturbances (psychotic reactions) (see Section 2: Take special care with Ciprofloxacin Bayer)
- decreased skin sensitivity, tremor, migraine, disorder of sense of smell (olfactory disorders)
- tinnitus, impaired hearing
- fainting, inflammation of the blood vessel (vasculitis)
- shortness of breath including asthmatic symptoms
- pancreatitis
- hepatitis, death of liver cells (liver necrosis) very rarely leading to life-threatening liver failure
- sensitivity to light (see Section 2: Take special care with Ciprofloxacin Bayer), small, pin-point bleeding under the skin (petechiae)

- muscle pain, inflammation of the joints, increased muscle tone, cramping, tendon rupture – especially of the large tendon at the back of the ankle (Achilles tendon) (see Section 2: Take special care with Ciprofloxacin Bayer)
- blood or crystals in the urine (see Section 2: Take special care with Ciprofloxacin Bayer), urinary tract inflammation
- excessive sweating
- abnormal levels of a clotting factor (prothromibin) increased levels of the enzyme amylase

Very rare side effects (less than 1 in every 10,000 people are likely to get these):

- a special type of reduced red blood cell count (haemolytic anaemia); a dangerous drop in a type of
  white blood cells (agranulocytosis)
- severe allergic reaction (anaphylactic reaction, anaphylactic shock, serum sickness) which can be fatal (see Section 2: Take special care with Ciprofloxacin Bayer)
- disturbed coordination, unsteady walk (gait disturbance), pressure on the brain (intracranial pressure)
- visual colour distortions
- various skin eruptions or rashes (e.g. the potentially fatal Stevens-Johnson syndrome or toxic epidermal necrolysis)
- muscle weakness, tendon inflammation, worsening of the symptoms of myasthenia gravis (see Section 2: Take special care with Ciprofloxacin Bayer)

Frequency not known (cannot be estimated from the available data)
- troubles associated with the nervous system such as pain, burning, tingling, numbness and/ or weakness in extremities
- severe cardiac rhythm abnormalities, irregular heart beat (Torsades de Pointes)

5. HOW TO STORE CIPROFLOXACIN BAYER

[To be completed nationally]

Keep out of the reach and sight of children.

Do not use Ciprofloxacin Bayer after the expiry date which is stated on the carton after "EXP": The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ciprofloxacin Bayer contains

[To be completed nationally]

What Ciprofloxacin Bayer looks like and contents of the pack

Solution for infusion
[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

Belgium:	Ciproxine
Denmark:	Ciproxin
Estonia:	Ciproxin
Finland:	Ciproxin
France:	Ciflox
Greece:	Ciproxin
Iceland	Ciproxin
Ireland:	Ciproxin
Italy:	Ciproxin
Luxembourg:	Ciproxine
Norway:	Ciproxin
Portugal:	Ciproxina
Sweden:	Ciproxin
United Kingdom	Ciproxin

This leaflet was last approved in {MM/YYYY}

[To be completed nationally]

Advice/medical education

Antibiotics are used to cure bacterial infections. They are ineffective against viral infections.
If your doctor has prescribed antibiotics, you need them precisely for your current illness.
Despite antibiotics, some bacteria may survive or grow. This phenomenon is called resistance: some antibiotic treatments become ineffective.
Misuse of antibiotics increases resistance. You may even help bacteria become resistant and therefore delay your cure or decrease antibiotic efficacy if you do not respect appropriate:
- dosage
- schedules
- duration of treatment

Consequently, to preserve the efficacy of this drug:
1 - Use antibiotics only when prescribed.
2 - Strictly follow the prescription.
3 - Do not re-use an antibiotic without medical prescription, even if you want to treat a similar illness.
4 - Never give your antibiotic to another person; maybe it is not adapted to her/his illness.
5 - After completion of treatment, return all unused drugs to your chemist's shop to ensure they will be disposed of correctly

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The following information is intended for medical or healthcare professionals only

Ciprofloxacin Bayer should be administered by intravenous infusion. For children, the infusion duration is 60 minutes. In adult patients, infusion time is 60 minutes for 400 mg Ciprofloxacin Bayer and 30 minutes for 200 mg Ciprofloxacin Bayer. Slow infusion into a large vein will minimise patient discomfort and reduce the risk of venous irritation. The infusion solution can be infused either directly or after mixing with other compatible infusion solutions.

Unless compatibility with other infusion solutions/drugs has been confirmed, the infusion solution must always be administered separately. The visual signs of incompatibility are e.g. precipitation, clouding, and discolouration.

Incompatibility appears with all infusion solutions/drugs that are physically or chemically unstable at the pH of the solution (e.g. penicillins, heparin solutions), especially in combination with solutions adjusted to an alkaline pH (pH of the ciprofloxacin infusion solutions: 3.5-4.6).

After intravenous initiation of treatment, the treatment can be continued orally as well.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ciprofloxacin Bayer and associated names (see Annex I) 400 mg / 200 mL solution for infusion
[See Annex I - To be completed nationally]

Ciprofloxacin

Read all of this leaflet carefully before you are given this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT CIPROFLOXACIN BAYER IS AND WHAT IT IS USED FOR

Ciprofloxacin Bayer is an antibiotic belonging to the fluoroquinolone family. The active substance is ciprofloxacin. Ciprofloxacin works by killing bacteria that cause infections. It only works with specific strains of bacteria.

Adults

Ciprofloxacin Bayer is used in adults to treat the following bacterial infections:

- respiratory tract infections
- long lasting or recurring ear or sinus infections
- urinary tract infections
- infections of the testicles
- genital organ infections in women
- gastro-intestinal tract infections and intra-abdominal infections
- skin and soft tissue infections
- bone and joint infections
- to treat infections in patients with a very low white blood cell count (neutropenia)
- to prevent infections in patients with a very low white blood cell count (neutropenia)
- anthrax inhalation exposure

If you have a severe infection or one that is caused by more than one type of bacterium, you may be given additional antibiotic treatment in addition to Ciprofloxacin Bayer.

Children and adolescents

Ciprofloxacin Bayer is used in children and adolescents, under specialist medical supervision, to treat the following bacterial infections:

- lung and bronchial infections in children and adolescents suffering from cystic fibrosis
- complicated urinary tract infections, including infections that have reached the kidneys (pyelonephritis)
- anthrax inhalation exposure

Ciprofloxacin Bayer may also be used to treat other specific severe infections in children and adolescents when your doctor considered this necessary.

2. BEFORE YOU ARE GIVEN CIPROFLOXACIN BAYER

You must not be given Ciprofloxacin Bayer if you are:

- allergic (hypersensitive) to the active substance, to other quinolone drugs or to any of the other ingredients of Ciprofloxacin Bayer (see section 6)
- taking tizanidine (see Section 2: Taking other medicines)

Take special care with Ciprofloxacin Bayer

Before you are given Ciprofloxacin Bayer

Tell your doctor if you:

- have ever had kidney problems because your treatment may need to be adjusted
- suffer from epilepsy or other neurological conditions
- have a history of tendon problems during previous treatment with antibiotics such as Ciprofloxacin Bayer
- have myasthenia gravis (a type of muscle weakness)
- have a history of abnormal heart rhythms (arrythmias)

While under treatment with Ciprofloxacin Bayer

Tell your doctor immediately, if any of the following occurs **during treatment with Ciprofloxacin Bayer**. Your doctor will decide whether treatment with Ciprofloxacin Bayer needs to be stopped.

- **Severe, sudden allergic reaction** (an anaphylactic reaction/shock, angio-oedema). Even with the first dose, there is a rare chance that you may experience a severe allergic reaction with the following symptoms: tightness in the chest, feeling dizzy, feeling sick or faint, or experience dizziness on standing. **If this happens, tell your doctor immediately since the administration of Ciprofloxacin Bayer will have to be stopped.**

- **Pain and swelling in the joints, and tendinitis** may occur occasionally, particularly if you are elderly and are also being treated with corticosteroids. At the first sign of any pain or inflammation Ciprofloxacin Bayer will have to be stopped, rest the painful area. Avoid any unnecessary exercise as this might increase the risk of a tendon rupture.

- If you suffer from **epilepsy** or other **neurological conditions** such as cerebral ischemia or stroke, you may experience side effects associated with the central nervous system. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience **psychiatric reactions** after first administration of ciprofloxacin. If you suffer from **depression** or **psychosis**, your symptoms may become worse under treatment with Ciprofloxacin Bayer. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience symptoms of neuropathy such as pain, burning, tingling, numbness and/or weakness. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- **Diarrhoea** may develop while you are on antibiotics, including Ciprofloxacin Bayer, or even several weeks after you have stopped using them. If it becomes severe or persistent or you notice that your stool contains blood or mucus tell your doctor immediately. Ciprofloxacin Bayer treatment will have to be stopped immediately, as this can be life-threatening. Do not take medicines that stop or slow down bowel movements.

- Tell the doctor or laboratory staff that you are taking Ciprofloxacin Bayer if you have to provide a **blood or urine** sample.

- Ciprofloxacin Bayer may cause **liver damage**. If you notice any symptoms such as loss of appetite, jaundice (yellowing of the skin), dark urine, itching, or tenderness of the stomach, Ciprofloxacin Bayer must be stopped immediately.

- Ciprofloxacin Bayer may cause a reduction in the number of white blood cells and your **resistance to infection may be decreased**. If you experience an infection with symptoms such as fever and serious deterioration of your general condition, or fever with local infection symptoms such as sore throat/pharynx/mouth or urinary problems you should see your doctor immediately. A blood test will be taken to check possible reduction of white blood cells (agranulocytosis). It is important to inform your doctor about your medicine.

- Tell your doctor if you or a member of your family is known to have a deficiency in glucose-6-phosphate dehydrogenase (G6PD), since you may experience a risk of anemia with ciprofloxacin.

- Your skin becomes more **sensitive to sunlight or ultraviolet (UV) light** under treatment with Ciprofloxacin Bayer. Avoid exposure to strong sunlight or artificial UV light such as sunbeds.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Do not use Ciprofloxacin Bayer together with tizanidine, because this may cause side effects such as low blood pressure and sleepiness (see Section 2: "**You must not be given Ciprofloxacin Bayer if you are**").

The following medicines are known to interact with Ciprofloxacin Bayer in your body. Using Ciprofloxacin Bayer together with these medicines can influence the therapeutic effect of these medicines. It can also increase the probability of experiencing side effects.

Tell your doctor if you are taking:

- warfarin or other oral anti-coagulants (to thin the blood)
- probenecid (for gout)
- methotrexate (for certain types of cancer, psoriasis, rheumatoid arthritis)
- theophylline (for breathing problems)
- tizanidine (for muscle spasticity in multiple sclerosis)
- clozapine (an antipsychotic)
- ropinirole (for Parkinson's disease)
- phenytoin (for epilepsy)

Ciprofloxacin Bayer may **increase** the levels of the following medicines in your blood:

- pentoxifylline (for circulatory disorders)
- caffeine

Taking Ciprofloxacin Bayer with food and drink

Food and drink does not affect your treatment with Ciprofloxacin Bayer.

Pregnancy and breast-feeding

It is preferable to avoid the use of Ciprofloxacin Bayer during pregnancy. Tell your doctor if you are planning to get pregnant.

Do not take Ciprofloxacin Bayer during breast feeding because ciprofloxacin is excreted in breast milk and can be harmful for your child.

Driving and using machines

Ciprofloxacin Bayer may make you feel less alert. Some neurological adverse events can occur. Therefore, make sure you know how you react to Ciprofloxacin Bayer before driving a vehicle or operating machinery. If in doubt, talk to your doctor.

Important information about some of the ingredients of Ciprofloxacin Bayer
Glucose
[To be completed nationally]

3. HOW TO USE CIPROFLOXACIN BAYER

Your doctor will explain to you exactly how much Ciprofloxacin Bayer you will be given as well as how often and for how long. This will depend on the type of infection you have and how bad it is.

Tell your doctor if you suffer from kidney problems because your dose may need to be adjusted.

Treatment usually lasts between 5 and 21 days, but may be longer for severe infections.

Your doctor will give you each dose by slow infusion through a vein into your bloodstream. For children, the infusion duration is 60 minutes. In adult patients, infusion time is 60 minutes for 400 mg Ciprofloxacin Bayer and 30 minutes for 200 mg Ciprofloxacin Bayer. Administering the infusion slowly helps prevent immediate side effects occurring.

Remember to drink plenty of fluids while you are taking Ciprofloxacin Bayer.

If you stop your course of Ciprofloxacin Bayer

- It is important that you **finish the course of treatment** even if you begin to feel better after a few days. If you stop using this medicine too soon your infection may not be completely cured and the symptoms of the infection may return or get worse. You might also develop resistance to the antibiotic.

If you have any more questions about the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ciprofloxacin Bayer can cause side effects, although not everybody gets them.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

Common side effects (between 1 and 10 in every 100 people are likely to get these):

- nausea, diarrhoea, vomiting
- joint pains in children
- local reaction at the injection site, rash
- temporary increased amounts of substances in the blood (transaminases)

Uncommon side effects (between 1 and 10 in every 1,000 people are likely to get these):

- fungal superinfections
- a high concentration of eosinophils, a type of white blood cell, increased or decreased amounts of a blood cloting factor (thrombocytes)
- loss of appetite (anorexia)
- hyperactivity, agitation, confusion, disorientation, hallucinations
- headache, dizziness, sleeping problems, taste disorders, pins and needles, unusual sensitivity to stimuli of the senses, seizures (see Section 2: Take special care with Ciprofloxacin Bayer), giddiness
- eyesight problems
- loss of hearing
- rapid heartbeat (tachycardia)
- expansion of the blood vessels (vasodilation), low blood pressure
- abdominal pain, digestive problems such as stomach upset (indigestion/heartburn), wind
- liver disorders, increased amounts of one substance in the blood (bilirubin), jaundice (cholestatic icterus)
- itching, hives
- joint pain in adults
- poor kidney function, kidney failure
- pains in your muscles and bones, feeling unwell (asthenia), fever, fluid retention
- increase in blood alkaline phosphatase (a certain substance in the blood)

Rare side effects (between 1 and 10 in every 10,000 people are likely to get these):

- inflammation of the bowel (colitis) linked to antibiotic use (can be fatal in rare cases) (see Section 2: Take special care with Ciprofloxacin Bayer)
- changes to the blood count (leukopenia, leukocytosis, neutropenia, anaemia), a drop in the number of red and white blood cells and platelets (pancytopenia), which may be fatal, bone-marrow depression which may also be fatal (see Section 2: Take special care with Ciprofloxacin Bayer)
- allergic reaction, allergic swelling (oedema), rapid swelling of the skin and mucous membranes (angiooedema), severe allergic reaction (anaphylactic shock) which can be life-threatening (see Section 2: Take special care with Ciprofloxacin Bayer)
- increased blood sugar (hyperglycemia)
- anxiety reaction, strange dreams, depression, mental disturbances (psychotic reactions) (see Section 2: Take special care with Ciprofloxacin Bayer)
- decreased skin sensitivity, tremor, migraine, disorder of sense of smell (olfactory disorders)
- tinnitus, impaired hearing
- fainting, inflammation of the blood vessel (vasculitis)
- shortness of breath including asthmatic symptoms
- pancreatitis
- hepatitis, death of liver cells (liver necrosis) very rarely leading to life-threatening liver failure
- sensitivity to light (see Section 2: Take special care with Ciprofloxacin Bayer), small, pin-point bleeding under the skin (petechiae)

- muscle pain, inflammation of the joints, increased muscle tone, cramping, tendon rupture – especially of the large tendon at the back of the ankle (Achilles tendon) (see Section 2: Take special care with Ciprofloxacin Bayer)
- blood or crystals in the urine (see Section 2: Take special care with Ciprofloxacin Bayer), urinary tract inflammation
- excessive sweating
- abnormal levels of a clotting factor (prothromibin) increased levels of the enzyme amylase

Very rare side effects (less than 1 in every 10,000 people are likely to get these):

- a special type of reduced red blood cell count (haemolytic anaemia); a dangerous drop in a type of
  white blood cells (agranulocytosis)
- severe allergic reaction (anaphylactic reaction, anaphylactic shock, serum sickness) which can be fatal (see Section 2: Take special care with Ciprofloxacin Bayer)
- disturbed coordination, unsteady walk (gait disturbance), pressure on the brain (intracranial pressure)
- visual colour distortions
- various skin eruptions or rashes (e.g. the potentially fatal Stevens-Johnson syndrome or toxic epidermal necrolysis)
- muscle weakness, tendon inflammation, worsening of the symptoms of myasthenia gravis (see Section 2: Take special care with Ciprofloxacin Bayer)

Frequency not known (cannot be estimated from the available data)
- troubles associated with the nervous system such as pain, burning, tingling, numbness and/ or weakness in extremities
- severe cardiac rhythm abnormalities, irregular heart beat (Torsades de Pointes)

5. HOW TO STORE CIPROFLOXACIN BAYER

[To be completed nationally]

Keep out of the reach and sight of children.

Do not use Ciprofloxacin Bayer after the expiry date which is stated on the carton after "EXP": The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ciprofloxacin Bayer contains

[To be completed nationally]

What Ciprofloxacin Bayer looks like and contents of the pack

Solution for infusion
[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

Belgium:	Ciproxine
Denmark:	Ciproxin
Estonia:	Ciproxin
Finland:	Ciproxin
France:	Ciflox
Greece:	Ciproxin
Iceland:	Ciproxin
Ireland :	Ciproxin
Italy:	Ciproxin
Luxembourg:	Ciproxine
Norway:	Ciproxin
Sweden:	Ciproxin
United Kingdom:	Ciproxin

This leaflet was last approved in {MM/YYYY}

[To be completed nationally]

Advice/medical education

Antibiotics are used to cure bacterial infections. They are ineffective against viral infections.
If your doctor has prescribed antibiotics, you need them precisely for your current illness.
Despite antibiotics, some bacteria may survive or grow. This phenomenon is called resistance: some antibiotic treatments become ineffective.
Misuse of antibiotics increases resistance. You may even help bacteria become resistant and therefore delay your cure or decrease antibiotic efficacy if you do not respect appropriate:
- dosage
- schedules
- duration of treatment

Consequently, to preserve the efficacy of this drug:
1 - Use antibiotics only when prescribed.
2 - Strictly follow the prescription.
3 - Do not re-use an antibiotic without medical prescription, even if you want to treat a similar illness.
4 - Never give your antibiotic to another person; maybe it is not adapted to her/his illness.
5 - After completion of treatment, return all unused drugs to your chemist's shop to ensure they will be disposed of correctly

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The following information is intended for medical or healthcare professionals only

Ciprofloxacin Bayer should be administered by intravenous infusion. For children, the infusion duration is 60 minutes. In adult patients, infusion time is 60 minutes for 400 mg Ciprofloxacin Bayer and 30 minutes for 200 mg Ciprofloxacin Bayer. Slow infusion into a large vein will minimise patient discomfort and reduce the risk of venous irritation. The infusion solution can be infused either directly or after mixing with other compatible infusion solutions.

Unless compatibility with other infusion solutions/drugs has been confirmed, the infusion solution must

always be administered separately. The visual signs of incompatibility are e.g. precipitation, clouding, and discolouration.

Incompatibility appears with all infusion solutions/drugs that are physically or chemically unstable at the pH of the solution (e.g. penicillins, heparin solutions), especially in combination with solutions adjusted to an alkaline pH (pH of the ciprofloxacin infusion solutions: 3.5-4.6).

After intravenous initiation of treatment, the treatment can be continued orally as well.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ciprofloxacin Bayer and associated names (see Annex I) 100 mg/50 mL solution for infusion
[See Annex I - To be completed nationally]

Ciprofloxacin

Read all of this leaflet carefully before you are given this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT CIPROFLOXACIN BAYER IS AND WHAT IT IS USED FOR

Ciprofloxacin Bayer is an antibiotic belonging to the fluoroquinolone family. The active substance is ciprofloxacin. Ciprofloxacin works by killing bacteria that cause infections. It only works with specific strains of bacteria.

Adults

Ciprofloxacin Bayer is used in adults to treat the following bacterial infections:

- respiratory tract infections
- long lasting or recurring ear or sinus infections
- urinary tract infections
- infections of the testicles
- genital organ infections in women
- gastro-intestinal tract infections and intra-abdominal infections
- skin and soft tissue infections
- bone and joint infections
- to treat infections in patients with a very low white blood cell count (neutropenia)
- to prevent infections in patients with a very low white blood cell count (neutropenia)
- anthrax inhalation exposure

If you have a severe infection or one that is caused by more than one type of bacterium, you may be given additional antibiotic treatment in addition to Ciprofloxacin Bayer.

Children and adolescents

Ciprofloxacin Bayer is used in children and adolescents, under specialist medical supervision, to treat the following bacterial infections:

- lung and bronchial infections in children and adolescents suffering from cystic fibrosis
- complicated urinary tract infections, including infections that have reached the kidneys (pyelonephritis)
- anthrax inhalation exposure

Ciprofloxacin Bayer may also be used to treat other specific severe infections in children and adolescents when your doctor considered this necessary.

2. BEFORE YOU ARE GIVEN CIPROFLOXACIN BAYER

You must not be given Ciprofloxacin Bayer if you are:

- allergic (hypersensitive) to the active substance, to other quinolone drugs or to any of the other ingredients of Ciprofloxacin Bayer (see section 6)
- taking tizanidine (see Section 2: Taking other medicines)

Take special care with Ciprofloxacin Bayer

Before you are given Ciprofloxacin Bayer

Tell your doctor if you:

- have ever had kidney problems because your treatment may need to be adjusted
- suffer from epilepsy or other neurological conditions
- have a history of tendon problems during previous treatment with antibiotics such as Ciprofloxacin Bayer
- have myasthenia gravis (a type of muscle weakness)
- have a history of abnormal heart rhythms (arrythmias)

While under treatment with Ciprofloxacin Bayer

Tell your doctor immediately, if any of the following occurs **during treatment with Ciprofloxacin Bayer**. Your doctor will decide whether treatment with Ciprofloxacin Bayer needs to be stopped.

- **Severe, sudden allergic reaction** (an anaphylactic reaction/shock, angio-oedema). Even with the first dose, there is a rare chance that you may experience a severe allergic reaction with the following symptoms: tightness in the chest, feeling dizzy, feeling sick or faint, or experience dizziness on standing. **If this happens, tell your doctor immediately since the administration of Ciprofloxacin Bayer will have to be stopped.**

- **Pain and swelling in the joints, and tendinitis** may occur occasionally, particularly if you are elderly and are also being treated with corticosteroids. At the first sign of any pain or inflammation Ciprofloxacin Bayer will have to be stopped, rest the painful area. Avoid any unnecessary exercise as this might increase the risk of a tendon rupture.

- If you suffer from **epilepsy** or other **neurological conditions** such as cerebral ischemia or stroke, you may experience side effects associated with the central nervous system. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience **psychiatric reactions** after first administration of ciprofloxacin. If you suffer from **depression** or **psychosis**, your symptoms may become worse under treatment with Ciprofloxacin Bayer. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience symptoms of neuropathy such as pain, burning, tingling, numbness and/or weakness. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- **Diarrhoea** may develop while you are on antibiotics, including Ciprofloxacin Bayer, or even several weeks after you have stopped using them. If it becomes severe or persistent or you notice that your stool contains blood or mucus tell your doctor immediately. Ciprofloxacin Bayer treatment will have to be stopped immediately, as this can be life-threatening. Do not take medicines that stop or slow down bowel movements.

- Tell the doctor or laboratory staff that you are taking Ciprofloxacin Bayer if you have to provide a **blood or urine sample**.

- Ciprofloxacin Bayer may cause **liver damage**. If you notice any symptoms such as loss of appetite, jaundice (yellowing of the skin), dark urine, itching, or tenderness of the stomach, Ciprofloxacin Bayer must be stopped immediately.

- Ciprofloxacin Bayer may cause a reduction in the number of white blood cells and your **resistance to infection may be decreased**. If you experience an infection with symptoms such as fever and serious deterioration of your general condition, or fever with local infection symptoms such as sore throat/pharynx/mouth or urinary problems you should see your doctor immediately. A blood test will be taken to check possible reduction of white blood cells (agranulocytosis). It is important to inform your doctor about your medicine.

- Tell your doctor if you or a member of your family is known to have a deficiency in glucose-6-phosphate dehydrogenase (G6PD), since you may experience a risk of anemia with ciprofloxacin.

- Your skin becomes more **sensitive to sunlight or ultraviolet (UV) light** under treatment with Ciprofloxacin Bayer. Avoid exposure to strong sunlight or artificial UV light such as sunbeds.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Do not use Ciprofloxacin Bayer together with tizanidine, because this may cause side effects such as low blood pressure and sleepiness (see Section 2: "**You must not be given Ciprofloxacin Bayer if you are**").

The following medicines are known to interact with Ciprofloxacin Bayer in your body. Using Ciprofloxacin Bayer together with these medicines can influence the therapeutic effect of these medicines. It can also increase the probability of experiencing side effects.

Tell your doctor if you are taking:

- warfarin or other oral anti-coagulants (to thin the blood)
- probenecid (for gout)
- methotrexate (for certain types of cancer, psoriasis, rheumatoid arthritis)
- theophylline (for breathing problems)
- tizanidine (for muscle spasticity in multiple sclerosis)
- clozapine (an antipsychotic)
- ropinirole (for Parkinson's disease)
- phenytoin (for epilepsy)

Ciprofloxacin Bayer may **increase** the levels of the following medicines in your blood:

- pentoxifylline (for circulatory disorders)
- caffeine

Taking Ciprofloxacin Bayer with food and drink

Food and drink does not affect your treatment with Ciprofloxacin Bayer.

Pregnancy and breast-feeding

It is preferable to avoid the use of Ciprofloxacin Bayer during pregnancy. Tell your doctor if you are planning to get pregnant.

Do not take Ciprofloxacin Bayer during breast feeding because ciprofloxacin is excreted in breast milk and can be harmful for your child.

Driving and using machines

Ciprofloxacin Bayer may make you feel less alert. Some neurological adverse events can occur. Therefore, make sure you know how you react to Ciprofloxacin Bayer before driving a vehicle or operating machinery. If in doubt, talk to your doctor.

Important information about some of the ingredients of Ciprofloxacin Bayer
Sodium
[To be completed nationally]

3 HOW TO USE CIPROFLOXACIN BAYER

Your doctor will explain to you exactly how much Ciprofloxacin Bayer you will be given as well as how often and for how long. This will depend on the type of infection you have and how bad it is.

Tell your doctor if you suffer from kidney problems because your dose may need to be adjusted.

Treatment usually lasts between 5 and 21 days, but may be longer for severe infections.

Your doctor will give you each dose by slow infusion through a vein into your bloodstream. For children, the infusion duration is 60 minutes. In adult patients, infusion time is 60 minutes for 400 mg Ciprofloxacin Bayer and 30 minutes for 200 mg Ciprofloxacin Bayer. Administering the infusion slowly helps prevent immediate side effects occurring.

Remember to drink plenty of fluids while you are taking Ciprofloxacin Bayer.

If you stop your course of Ciprofloxacin Bayer

- It is important that you **finish the course of treatment** even if you begin to feel better after a few days. If you stop using this medicine too soon your infection may not be completely cured and the symptoms of the infection may return or get worse. You might also develop resistance to the antibiotic.

If you have any more questions about the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ciprofloxacin Bayer can cause side effects, although not everybody gets them.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

Common side effects (between 1 and 10 in every 100 people are likely to get these):

- nausea, diarrhoea, vomiting
- joint pains in children
- local reaction at the injection site, rash
- temporary increased amounts of substances in the blood (transaminases)

Uncommon side effects (between 1 and 10 in every 1,000 people are likely to get these):

- fungal superinfections
- a high concentration of eosinophils, a type of white blood cell, increased or decreased amounts of a blood cloting factor (thrombocytes)
- loss of appetite (anorexia)
- hyperactivity, agitation, confusion, disorientation, hallucinations
- headache, dizziness, sleeping problems, taste disorders, pins and needles, unusual sensitivity to stimuli of the senses, seizures (see Section 2: Take special care with Ciprofloxacin Bayer), giddiness
- eyesight problems
- loss of hearing
- rapid heartbeat (tachycardia)
- expansion of the blood vessels (vasodilation), low blood pressure
- abdominal pain, digestive problems such as stomach upset (indigestion/heartburn), wind
- liver disorders, increased amounts of one substance in the blood (bilirubin), jaundice (cholestatic icterus)
- itching, hives
- joint pain in adults
- poor kidney function, kidney failure
- pains in your muscles and bones, feeling unwell (asthenia), fever, fluid retention
- increase in blood alkaline phosphatase (a certain substance in the blood)

Rare side effects (between 1 and 10 in every 10,000 people are likely to get these):

- inflammation of the bowel (colitis) linked to antibiotic use (can be fatal in rare cases) (see Section 2: Take special care with Ciprofloxacin Bayer)
- changes to the blood count (leukopenia, leukocytosis, neutropenia, anaemia), a drop in the number of red and white blood cells and platelets (pancytopenia), which may be fatal, bone-marrow depression which may also be fatal (see Section 2: Take special care with Ciprofloxacin Bayer)
- allergic reaction, allergic swelling (oedema), rapid swelling of the skin and mucous membranes (angiooedema), severe allergic reaction (anaphylactic shock) which can be life-threatening (see Section 2: Take special care with Ciprofloxacin Bayer)
- increased blood sugar (hyperglycemia)
- anxiety reaction, strange dreams, depression, mental disturbances (psychotic reactions) (see Section 2: Take special care with Ciprofloxacin Bayer)
- decreased skin sensitivity, tremor, migraine, disorder of sense of smell (olfactory disorders)
- tinnitus, impaired hearing
- fainting, inflammation of the blood vessel (vasculitis)
- shortness of breath including asthmatic symptoms
- pancreatitis
- hepatitis, death of liver cells (liver necrosis) very rarely leading to life-threatening liver failure

- sensitivity to light (see Section 2: Take special care with Ciprofloxacin Bayer), small, pin-point bleeding under the skin (petechiae)
- muscle pain, inflammation of the joints, increased muscle tone, cramping, tendon rupture – especially of the large tendon at the back of the ankle (Achilles tendon) (see Section 2: Take special care with Ciprofloxacin Bayer)
- blood or crystals in the urine (see Section 2: Take special care with Ciprofloxacin Bayer), urinary tract inflammation
- excessive sweating
- abnormal levels of a clotting factor (prothromibin) increased levels of the enzyme amylase

Very rare side effects (less than 1 in every 10,000 people are likely to get these):

- a special type of reduced red blood cell count (haemolytic anaemia); a dangerous drop in a type of
  white blood cells (agranulocytosis)
- severe allergic reaction (anaphylactic reaction, anaphylactic shock, serum sickness) which can be fatal (see Section 2: Take special care with Ciprofloxacin Bayer)
- disturbed coordination, unsteady walk (gait disturbance), pressure on the brain (intracranial pressure)
- visual colour distortions
- various skin eruptions or rashes (e.g. the potentially fatal Stevens-Johnson syndrome or toxic epidermal necrolysis)
- muscle weakness, tendon inflammation, worsening of the symptoms of myasthenia gravis (see Section 2: Take special care with Ciprofloxacin Bayer)

Frequency not known (cannot be estimated from the available data)
- troubles associated with the nervous system such as pain, burning, tingling, numbness and/ or weakness in extremities
- severe cardiac rhythm abnormalities, irregular heart beat (Torsades de Pointes)

5. HOW TO STORE CIPROFLOXACIN BAYER

[To be completed nationally]

Keep out of the reach and sight of children.

Do not use Ciprofloxacin Bayer after the expiry date which is stated on the carton after "EXP": The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ciprofloxacin Bayer contains

[To be completed nationally]

What Ciprofloxacin Bayer looks like and contents of the pack

Solution for infusion
[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria:	Ciproxin
Belgium:	Ciproxine
Czech Republic	Ciprobay
Germany:	Ciprobay; Ciprofloxacin ANTIBAC; Ciprofloxacin BAYER; Ciprofloxacin VITAL
Greece:	Ciproxin
Hungary:	Ciprobay
Ireland:	Ciproxin
Italy:	Ciproxin
Luxembourg:	Ciproxine
Malta:	Ciproxin
Netherlands:	Ciproxin
Poland:	Ciprobay
Slovak Republic:	Ciprobay
United Kingdom:	Ciproxin

This leaflet was last approved in {MM/YYYY}

[To be completed nationally]

Advice/medical education

Antibiotics are used to cure bacterial infections. They are ineffective against viral infections.
If your doctor has prescribed antibiotics, you need them precisely for your current illness.
Despite antibiotics, some bacteria may survive or grow. This phenomenon is called resistance: some antibiotic treatments become ineffective.
Misuse of antibiotics increases resistance. You may even help bacteria become resistant and therefore delay your cure or decrease antibiotic efficacy if you do not respect appropriate:
- dosage
- schedules
- duration of treatment

Consequently, to preserve the efficacy of this drug:
1 - Use antibiotics only when prescribed.
2 - Strictly follow the prescription.
3 - Do not re-use an antibiotic without medical prescription, even if you want to treat a similar illness.
4 - Never give your antibiotic to another person; maybe it is not adapted to her/his illness.
5 - After completion of treatment, return all unused drugs to your chemist's shop to ensure they will be disposed of correctly

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The following information is intended for medical or healthcare professionals only

Ciprofloxacin Bayer should be administered by intravenous infusion. For children, the infusion duration is 60 minutes. In adult patients, infusion time is 60 minutes for 400 mg Ciprofloxacin Bayer and 30 minutes for 200 mg Ciprofloxacin Bayer. Slow infusion into a large vein will minimise patient

discomfort and reduce the risk of venous irritation. The infusion solution can be infused either directly or after mixing with other compatible infusion solutions.

Unless compatibility with other infusion solutions/drugs has been confirmed, the infusion solution must always be administered separately. The visual signs of incompatibility are e.g. precipitation, clouding, and discolouration.

Incompatibility appears with all infusion solutions/drugs that are physically or chemically unstable at the pH of the solution (e.g. penicillin, heparin solutions), especially in combination with solutions adjusted to an alkaline pH (pH of the ciprofloxacin infusion solutions: 3.9-4.5).

After intravenous initiation of treatment, the treatment can be continued orally as well.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ciprofloxacin Bayer and associated names (see Annex I) 200 mg/100 mL solution for infusion
[See Annex I - To be completed nationally]

Ciprofloxacin

Read all of this leaflet carefully before you are given this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT CIPROFLOXACIN BAYER IS AND WHAT IT IS USED FOR

Ciprofloxacin Bayer is an antibiotic belonging to the fluoroquinolone family. The active substance is ciprofloxacin. Ciprofloxacin works by killing bacteria that cause infections. It only works with specific strains of bacteria.

Adults

Ciprofloxacin Bayer is used in adults to treat the following bacterial infections:

- respiratory tract infections
- long lasting or recurring ear or sinus infections
- urinary tract infections
- infections of the testicles
- genital organ infections in women
- gastro-intestinal tract infections and intra-abdominal infections
- skin and soft tissue infections
- bone and joint infections
- to treat infections in patients with a very low white blood cell count (neutropenia)
- to prevent infections in patients with a very low white blood cell count (neutropenia)
- anthrax inhalation exposure

If you have a severe infection or one that is caused by more than one type of bacterium, you may be given additional antibiotic treatment in addition to Ciprofloxacin Bayer.

Children and adolescents

Ciprofloxacin Bayer is used in children and adolescents, under specialist medical supervision, to treat the following bacterial infections:

- lung and bronchial infections in children and adolescents suffering from cystic fibrosis
- complicated urinary tract infections, including infections that have reached the kidneys (pyelonephritis)
- anthrax inhalation exposure

Ciprofloxacin Bayer may also be used to treat other specific severe infections in children and adolescents when your doctor considered this necessary.

2. BEFORE YOU ARE GIVEN CIPROFLOXACIN BAYER

You must not be given Ciprofloxacin Bayer if you are:

- allergic (hypersensitive) to the active substance, to other quinolone drugs or to any of the other ingredients of Ciprofloxacin Bayer (see section 6)
- taking tizanidine (see Section 2: Taking other medicines)

Take special care with Ciprofloxacin Bayer

Before you are given Ciprofloxacin Bayer

Tell your doctor if you:

- have ever had kidney problems because your treatment may need to be adjusted
- suffer from epilepsy or other neurological conditions
- have a history of tendon problems during previous treatment with antibiotics such as Ciprofloxacin Bayer
- have myasthenia gravis (a type of muscle weakness)
- have a history of abnormal heart rhythms (arrythmias)

While under treatment with Ciprofloxacin Bayer

Tell your doctor immediately, if any of the following occurs **during treatment with Ciprofloxacin Bayer**. Your doctor will decide whether treatment with Ciprofloxacin Bayer needs to be stopped.

- **Severe, sudden allergic reaction** (an anaphylactic reaction/shock, angio-oedema). Even with the first dose, there is a rare chance that you may experience a severe allergic reaction with the following symptoms: tightness in the chest, feeling dizzy, feeling sick or faint, or experience dizziness on standing. **If this happens, tell your doctor immediately since the administration of Ciprofloxacin Bayer will have to be stopped.**

- **Pain and swelling in the joints, and tendinitis** may occur occasionally, particularly if you are elderly and are also being treated with corticosteroids. At the first sign of any pain or inflammation Ciprofloxacin Bayer will have to be stopped, rest the painful area. Avoid any unnecessary exercise as this might increase the risk of a tendon rupture.

- If you suffer from **epilepsy** or other **neurological conditions** such as cerebral ischemia or stroke, you may experience side effects associated with the central nervous system. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience **psychiatric reactions** after first administration of ciprofloxacin. If you suffer from **depression** or **psychosis**, your symptoms may become worse under treatment with Ciprofloxacin Bayer. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience symptoms of neuropathy such as pain, burning, tingling, numbness and/or weakness. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- **Diarrhoea** may develop while you are on antibiotics, including Ciprofloxacin Bayer, or even several weeks after you have stopped using them. If it becomes severe or persistent or you notice that your stool contains blood or mucus tell your doctor immediately. Ciprofloxacin Bayer treatment will have to be stopped immediately, as this can be life-threatening. Do not take medicines that stop or slow down bowel movements.

- Tell the doctor or laboratory staff that you are taking Ciprofloxacin Bayer if you have to provide a **blood or urine sample**.

- Ciprofloxacin Bayer may cause **liver damage**. If you notice any symptoms such as loss of appetite, jaundice (yellowing of the skin), dark urine, itching, or tenderness of the stomach, Ciprofloxacin Bayer must be stopped immediately.

- Ciprofloxacin Bayer may cause a reduction in the number of white blood cells and your **resistance to infection may be decreased**. If you experience an infection with symptoms such as fever and serious deterioration of your general condition, or fever with local infection symptoms such as sore throat/pharynx/mouth or urinary problems you should see your doctor immediately. A blood test will be taken to check possible reduction of white blood cells (agranulocytosis). It is important to inform your doctor about your medicine.

- Tell your doctor if you or a member of your family is known to have a deficiency in glucose-6-phosphate dehydrogenase (G6PD), since you may experience a risk of anemia with ciprofloxacin.

- Your skin becomes more **sensitive to sunlight or ultraviolet (UV) light** under treatment with Ciprofloxacin Bayer. Avoid exposure to strong sunlight or artificial UV light such as sunbeds.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Do not use Ciprofloxacin Bayer together with tizanidine, because this may cause side effects such as low blood pressure and sleepiness (see Section 2: "**You must not be given Ciprofloxacin Bayer if you are**").

The following medicines are known to interact with Ciprofloxacin Bayer in your body. Using Ciprofloxacin Bayer together with these medicines can influence the therapeutic effect of these medicines. It can also increase the probability of experiencing side effects.

Tell your doctor if you are taking:

- warfarin or other oral anti-coagulants (to thin the blood)
- probenecid (for gout)
- methotrexate (for certain types of cancer, psoriasis, rheumatoid arthritis)
- theophylline (for breathing problems)
- tizanidine (for muscle spasticity in multiple sclerosis)
- clozapine (an antipsychotic)
- ropinirole (for Parkinson's disease)
- phenytoin (for epilepsy)

Ciprofloxacin Bayer may **increase** the levels of the following medicines in your blood:

- pentoxifylline (for circulatory disorders)
- caffeine

Taking Ciprofloxacin Bayer with food and drink

Food and drink does not affect your treatment with Ciprofloxacin Bayer.

Pregnancy and breast-feeding

It is preferable to avoid the use of Ciprofloxacin Bayer during pregnancy. Tell your doctor if you are planning to get pregnant.

Do not take Ciprofloxacin Bayer during breast feeding because ciprofloxacin is excreted in breast milk and can be harmful for your child.

Driving and using machines

Ciprofloxacin Bayer may make you feel less alert. Some neurological adverse events can occur. Therefore, make sure you know how you react to Ciprofloxacin Bayer before driving a vehicle or operating machinery. If in doubt, talk to your doctor.

Important information about some of the ingredients of Ciprofloxacin Bayer
Sodium
[To be completed nationally]

3. HOW TO USE CIPROFLOXACIN BAYER

Your doctor will explain to you exactly how much Ciprofloxacin Bayer you will be given as well as how often and for how long. This will depend on the type of infection you have and how bad it is.

Tell your doctor if you suffer from kidney problems because your dose may need to be adjusted.

Treatment usually lasts between 5 and 21 days, but may be longer for severe infections.

Your doctor will give you each dose by slow infusion through a vein into your bloodstream. For children, the infusion duration is 60 minutes. In adult patients, infusion time is 60 minutes for 400 mg Ciprofloxacin Bayer and 30 minutes for 200 mg Ciprofloxacin Bayer. Administering the infusion slowly helps prevent immediate side effects occurring.

Remember to drink plenty of fluids while you are taking Ciprofloxacin Bayer.

If you stop your course of Ciprofloxacin Bayer

- It is important that you **finish the course of treatment** even if you begin to feel better after a few days. If you stop using this medicine too soon your infection may not be completely cured and the symptoms of the infection may return or get worse. You might also develop resistance to the antibiotic.

If you have any more questions about the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ciprofloxacin Bayer can cause side effects, although not everybody gets them.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

Common side effects (between 1 and 10 in every 100 people are likely to get these):

- nausea, diarrhoea, vomiting
- joint pains in children
- local reaction at the injection site, rash
- temporary increased amounts of substances in the blood (transaminases)

Uncommon side effects (between 1 and 10 in every 1,000 people are likely to get these):

- fungal superinfections
- a high concentration of eosinophils, a type of white blood cell, increased or decreased amounts of a blood cloting factor (thrombocytes)
- loss of appetite (anorexia)
- hyperactivity, agitation, confusion, disorientation, hallucinations
- headache, dizziness, sleeping problems, taste disorders, pins and needles, unusual sensitivity to stimuli of the senses, seizures (see Section 2: Take special care with Ciprofloxacin Bayer), giddiness
- eyesight problems
- loss of hearing
- rapid heartbeat (tachycardia)
- expansion of the blood vessels (vasodilation), low blood pressure
- abdominal pain, digestive problems such as stomach upset (indigestion/heartburn), wind
- liver disorders, increased amounts of one substance in the blood (bilirubin), jaundice (cholestatic icterus)
- itching, hives
- joint pain in adults
- poor kidney function, kidney failure
- pains in your muscles and bones, feeling unwell (asthenia), fever, fluid retention
- increase in blood alkaline phosphatase (a certain substance in the blood)

Rare side effects (between 1 and 10 in every 10,000 people are likely to get these):

- inflammation of the bowel (colitis) linked to antibiotic use (can be fatal in rare cases) (see Section 2: Take special care with Ciprofloxacin Bayer)
- changes to the blood count (leukopenia, leukocytosis, neutropenia, anaemia), a drop in the number of red and white blood cells and platelets (pancytopenia), which may be fatal, bone-marrow depression which may also be fatal (see Section 2: Take special care with Ciprofloxacin Bayer)
- allergic reaction, allergic swelling (oedema), rapid swelling of the skin and mucous membranes (angiooedema), severe allergic reaction (anaphylactic shock) which can be life-threatening (see Section 2: Take special care with Ciprofloxacin Bayer)
- increased blood sugar (hyperglycemia)
- anxiety reaction, strange dreams, depression, mental disturbances (psychotic reactions) (see Section 2: Take special care with Ciprofloxacin Bayer)
- decreased skin sensitivity, tremor, migraine, disorder of sense of smell (olfactory disorders)
- tinnitus, impaired hearing
- fainting, inflammation of the blood vessel (vasculitis)
- shortness of breath including asthmatic symptoms
- pancreatitis
- hepatitis, death of liver cells (liver necrosis) very rarely leading to life-threatening liver failure
- sensitivity to light (see Section 2: Take special care with Ciprofloxacin Bayer), small, pin-point bleeding under the skin (petechiae)

- muscle pain, inflammation of the joints, increased muscle tone, cramping, tendon rupture – especially of the large tendon at the back of the ankle (Achilles tendon) (see Section 2: Take special care with Ciprofloxacin Bayer)
- blood or crystals in the urine (see Section 2: Take special care with Ciprofloxacin Bayer), urinary tract inflammation
- excessive sweating
- abnormal levels of a clotting factor (prothromibin) increased levels of the enzyme amylase

Very rare side effects (less than 1 in every 10,000 people are likely to get these):

- a special type of reduced red blood cell count (haemolytic anaemia); a dangerous drop in a type of
  white blood cells (agranulocytosis)
- severe allergic reaction (anaphylactic reaction, anaphylactic shock, serum sickness) which can be fatal (see Section 2: Take special care with Ciprofloxacin Bayer)
- disturbed coordination, unsteady walk (gait disturbance), pressure on the brain (intracranial pressure)
- visual colour distortions
- various skin eruptions or rashes (e.g. the potentially fatal Stevens-Johnson syndrome or toxic epidermal necrolysis)
- muscle weakness, tendon inflammation, worsening of the symptoms of myasthenia gravis (see Section 2: Take special care with Ciprofloxacin Bayer)

Frequency not known (cannot be estimated from the available data)
- troubles associated with the nervous system such as pain, burning, tingling, numbness and/ or weakness in extremities
- severe cardiac rhythm abnormalities, irregular heart beat (Torsades de Pointes)

5. HOW TO STORE CIPROFLOXACIN BAYER

[To be completed nationally]

Keep out of the reach and sight of children.

Do not use Ciprofloxacin Bayer after the expiry date which is stated on the carton after "EXP": The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ciprofloxacin Bayer contains

[To be completed nationally]

What Ciprofloxacin Bayer looks like and contents of the pack

Solution for infusion
[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria:	Ciproxin; Ciprofloxacine « BAYER »
Belgium:	Ciproxine
Bulgaria:	Ciprobay
Cyprus	Ciproxin
Czech Republic	Ciprobay
France:	Ciflox
Germany:	Ciprobay; Ciprofloxacin ANTIBAC; Ciprofloxacin BAYER; Ciprofloxacin VITAL
Greece:	Ciproxin
Hungary:	Ciprobay
Ireland:	Ciproxin
Italy:	Ciproxin
Luxembourg:	Ciproxine
Malta:	Ciproxin
Netherlands:	Ciproxin
Poland:	Ciprobay
Portugal:	Ciproxina
Romania:	Ciprobay
Slovak Republic:	Ciprobay
Slovenia:	Ciprobay
United Kingdom:	Ciproxin

This leaflet was last approved in {MM/YYYY}

[To be completed nationally]

Advice/medical education

Antibiotics are used to cure bacterial infections. They are ineffective against viral infections.
If your doctor has prescribed antibiotics, you need them precisely for your current illness.
Despite antibiotics, some bacteria may survive or grow. This phenomenon is called resistance: some antibiotic treatments become ineffective.
Misuse of antibiotics increases resistance. You may even help bacteria become resistant and therefore delay your cure or decrease antibiotic efficacy if you do not respect appropriate:
- dosage
- schedules
- duration of treatment

Consequently, to preserve the efficacy of this drug:
1 - Use antibiotics only when prescribed.
2 - Strictly follow the prescription.
3 - Do not re-use an antibiotic without medical prescription, even if you want to treat a similar illness.
4 - Never give your antibiotic to another person; maybe it is not adapted to her/his illness.
5 - After completion of treatment, return all unused drugs to your chemist's shop to ensure they will be disposed of correctly

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The following information is intended for medical or healthcare professionals only

Ciprofloxacin Bayer should be administered by intravenous infusion. For children, the infusion duration is 60 minutes. In adult patients, infusion time is 60 minutes for 400 mg Ciprofloxacin Bayer and 30 minutes for 200 mg Ciprofloxacin Bayer. Slow infusion into a large vein will minimise patient discomfort and reduce the risk of venous irritation. The infusion solution can be infused either directly or after mixing with other compatible infusion solutions.

Unless compatibility with other infusion solutions/drugs has been confirmed, the infusion solution must always be administered separately. The visual signs of incompatibility are e.g. precipitation, clouding, and discolouration.

Incompatibility appears with all infusion solutions/drugs that are physically or chemically unstable at the pH of the solution (e.g. penicillin, heparin solutions), especially in combination with solutions adjusted to an alkaline pH (pH of the ciprofloxacin infusion solutions: 3.9-4.5).

After intravenous initiation of treatment, the treatment can be continued orally as well.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ciprofloxacin Bayer and associated names (see Annex I) 400 mg/200 mL solution for infusion
[See Annex I - To be completed nationally]

Ciprofloxacin

Read all of this leaflet carefully before you are given this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT CIPROFLOXACIN BAYER IS AND WHAT IT IS USED FOR

Ciprofloxacin Bayer is an antibiotic belonging to the fluoroquinolone family. The active substance is ciprofloxacin. Ciprofloxacin works by killing bacteria that cause infections. It only works with specific strains of bacteria.

Adults

Ciprofloxacin Bayer is used in adults to treat the following bacterial infections:

- respiratory tract infections
- long lasting or recurring ear or sinus infections
- urinary tract infections
- infections of the testicles
- genital organ infections in women
- gastro-intestinal tract infections and intra-abdominal infections
- skin and soft tissue infections
- bone and joint infections
- to treat infections in patients with a very low white blood cell count (neutropenia)
- to prevent infections in patients with a very low white blood cell count (neutropenia)
- anthrax inhalation exposure

If you have a severe infection or one that is caused by more than one type of bacterium, you may be given additional antibiotic treatment in addition to Ciprofloxacin Bayer.

Children and adolescents

Ciprofloxacin Bayer is used in children and adolescents, under specialist medical supervision, to treat the following bacterial infections:

- lung and bronchial infections in children and adolescents suffering from cystic fibrosis
- complicated urinary tract infections, including infections that have reached the kidneys (pyelonephritis)
- anthrax inhalation exposure

Ciprofloxacin Bayer may also be used to treat other specific severe infections in children and adolescents when your doctor considered this necessary.

2. BEFORE YOU ARE GIVEN CIPROFLOXACIN BAYER

You must not be given Ciprofloxacin Bayer if you are:

- allergic (hypersensitive) to the active substance, to other quinolone drugs or to any of the other ingredients of Ciprofloxacin Bayer (see section 6)
- taking tizanidine (see Section 2: Taking other medicines)

Take special care with Ciprofloxacin Bayer

Before you are given Ciprofloxacin Bayer

Tell your doctor if you:

- have ever had kidney problems because your treatment may need to be adjusted
- suffer from epilepsy or other neurological conditions
- have a history of tendon problems during previous treatment with antibiotics such as Ciprofloxacin Bayer
- have myasthenia gravis (a type of muscle weakness)
- have a history of abnormal heart rhythms (arrythmias)

While under treatment with Ciprofloxacin Bayer

Tell your doctor immediately, if any of the following occurs **during treatment with Ciprofloxacin Bayer**. Your doctor will decide whether treatment with Ciprofloxacin Bayer needs to be stopped.

- **Severe, sudden allergic reaction** (an anaphylactic reaction/shock, angio-oedema). Even with the first dose, there is a rare chance that you may experience a severe allergic reaction with the following symptoms: tightness in the chest, feeling dizzy, feeling sick or faint, or experience dizziness on standing. **If this happens, tell your doctor immediately since the administration of Ciprofloxacin Bayer will have to be stopped.**

- **Pain and swelling in the joints, and tendinitis** may occur occasionally, particularly if you are elderly and are also being treated with corticosteroids. At the first sign of any pain or inflammation Ciprofloxacin Bayer will have to be stopped, rest the painful area. Avoid any unnecessary exercise as this might increase the risk of a tendon rupture.

- If you suffer from **epilepsy** or other **neurological conditions** such as cerebral ischemia or stroke, you may experience side effects associated with the central nervous system. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience **psychiatric reactions** after first administration of ciprofloxacin. If you suffer from **depression** or **psychosis**, your symptoms may become worse under treatment with Ciprofloxacin Bayer. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- You may experience symptoms of neuropathy such as pain, burning, tingling, numbness and/or weakness. If this happens, stop taking Ciprofloxacin Bayer and contact your doctor immediately.

- **Diarrhoea** may develop while you are on antibiotics, including Ciprofloxacin Bayer, or even several weeks after you have stopped using them. If it becomes severe or persistent or you notice that your stool contains blood or mucus tell your doctor immediately. Ciprofloxacin Bayer treatment will have to be stopped immediately, as this can be life-threatening. Do not take medicines that stop or slow down bowel movements.

- Tell the doctor or laboratory staff that you are taking Ciprofloxacin Bayer if you have to provide a **blood or urine sample**.

- Ciprofloxacin Bayer may cause **liver damage**. If you notice any symptoms such as loss of appetite, jaundice (yellowing of the skin), dark urine, itching, or tenderness of the stomach, Ciprofloxacin Bayer must be stopped immediately.

- Ciprofloxacin Bayer may cause a reduction in the number of white blood cells and your **resistance to infection may be decreased**. If you experience an infection with symptoms such as fever and serious deterioration of your general condition, or fever with local infection symptoms such as sore throat/pharynx/mouth or urinary problems you should see your doctor immediately. A blood test will be taken to check possible reduction of white blood cells (agranulocytosis). It is important to inform your doctor about your medicine.

- Tell your doctor if you or a member of your family is known to have a deficiency in glucose-6-phosphate dehydrogenase (G6PD), since you may experience a risk of anemia with ciprofloxacin.

- Your skin becomes more **sensitive to sunlight or ultraviolet (UV) light** under treatment with Ciprofloxacin Bayer. Avoid exposure to strong sunlight or artificial UV light such as sunbeds.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Do not use Ciprofloxacin Bayer together with tizanidine, because this may cause side effects such as low blood pressure and sleepiness (see Section 2: "**You must not be given Ciprofloxacin Bayer if you are**").

The following medicines are known to interact with Ciprofloxacin Bayer in your body. Using Ciprofloxacin Bayer together with these medicines can influence the therapeutic effect of these medicines. It can also increase the probability of experiencing side effects.

Tell your doctor if you are taking:

- warfarin or other oral anti-coagulants (to thin the blood)
- probenecid (for gout)
- methotrexate (for certain types of cancer, psoriasis, rheumatoid arthritis)
- theophylline (for breathing problems)
- tizanidine (for muscle spasticity in multiple sclerosis)
- clozapine (an antipsychotic)
- ropinirole (for Parkinson's disease)
- phenytoin (for epilepsy)

Ciprofloxacin Bayer may **increase** the levels of the following medicines in your blood:

- pentoxifylline (for circulatory disorders)
- caffeine

Taking Ciprofloxacin Bayer with food and drink

Food and drink does not affect your treatment with Ciprofloxacin Bayer.

Pregnancy and breast-feeding

It is preferable to avoid the use of Ciprofloxacin Bayer during pregnancy. Tell your doctor if you are planning to get pregnant.

Do not take Ciprofloxacin Bayer during breast feeding because ciprofloxacin is excreted in breast milk and can be harmful for your child.

Driving and using machines

Ciprofloxacin Bayer may make you feel less alert. Some neurological adverse events can occur. Therefore, make sure you know how you react to Ciprofloxacin Bayer before driving a vehicle or operating machinery. If in doubt, talk to your doctor.

Important information about some of the ingredients of Ciprofloxacin Bayer
Sodium
[To be completed nationally]

3. HOW TO USE CIPROFLOXACIN BAYER

Your doctor will explain to you exactly how much Ciprofloxacin Bayer you will be given as well as how often and for how long. This will depend on the type of infection you have and how bad it is.

Tell your doctor if you suffer from kidney problems because your dose may need to be adjusted.

Treatment usually lasts between 5 and 21 days, but may be longer for severe infections.

Your doctor will give you each dose by slow infusion through a vein into your bloodstream. For children, the infusion duration is 60 minutes. In adult patients, infusion time is 60 minutes for 400 mg Ciprofloxacin Bayer and 30 minutes for 200 mg Ciprofloxacin Bayer. Administering the infusion slowly helps prevent immediate side effects occurring.

Remember to drink plenty of fluids while you are taking Ciprofloxacin Bayer.

If you stop your course of Ciprofloxacin Bayer

- It is important that you **finish the course of treatment** even if you begin to feel better after a few days. If you stop using this medicine too soon your infection may not be completely cured and the symptoms of the infection may return or get worse. You might also develop resistance to the antibiotic.

If you have any more questions about the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ciprofloxacin Bayer can cause side effects, although not everybody gets them.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

Common side effects (between 1 and 10 in every 100 people are likely to get these):

- nausea, diarrhoea, vomiting
- joint pains in children
- local reaction at the injection site, rash
- temporary increased amounts of substances in the blood (transaminases)

Uncommon side effects (between 1 and 10 in every 1,000 people are likely to get these):

- fungal superinfections
- a high concentration of eosinophils, a type of white blood cell, increased or decreased amounts of a blood cloting factor (thrombocytes)
- loss of appetite (anorexia)
- hyperactivity, agitation, confusion, disorientation, hallucinations
- headache, dizziness, sleeping problems, taste disorders, pins and needles, unusual sensitivity to stimuli of the senses, seizures (see Section 2: Take special care with Ciprofloxacin Bayer), giddiness
- eyesight problems
- loss of hearing
- rapid heartbeat (tachycardia)
- expansion of the blood vessels (vasodilation), low blood pressure
- abdominal pain, digestive problems such as stomach upset (indigestion/heartburn), wind
- liver disorders, increased amounts of one substance in the blood (bilirubin), jaundice (cholestatic icterus)
- itching, hives
- joint pain in adults
- poor kidney function, kidney failure
- pains in your muscles and bones, feeling unwell (asthenia), fever, fluid retention
- increase in blood alkaline phosphatase (a certain substance in the blood)

Rare side effects (between 1 and 10 in every 10,000 people are likely to get these):

- inflammation of the bowel (colitis) linked to antibiotic use (can be fatal in rare cases) (see Section 2: Take special care with Ciprofloxacin Bayer)
- changes to the blood count (leukopenia, leukocytosis, neutropenia, anaemia), a drop in the number of red and white blood cells and platelets (pancytopenia), which may be fatal, bone-marrow depression which may also be fatal (see Section 2: Take special care with Ciprofloxacin Bayer)
- allergic reaction, allergic swelling (oedema), rapid swelling of the skin and mucous membranes (angiooedema), severe allergic reaction (anaphylactic shock) which can be life-threatening (see Section 2: Take special care with Ciprofloxacin Bayer)
- increased blood sugar (hyperglycemia)
- anxiety reaction, strange dreams, depression, mental disturbances (psychotic reactions) (see Section 2: Take special care with Ciprofloxacin Bayer)
- decreased skin sensitivity, tremor, migraine, disorder of sense of smell (olfactory disorders)
- tinnitus, impaired hearing
- fainting, inflammation of the blood vessel (vasculitis)
- shortness of breath including asthmatic symptoms
- pancreatitis

- hepatitis, death of liver cells (liver necrosis) very rarely leading to life-threatening liver failure
- sensitivity to light (see Section 2: Take special care with Ciprofloxacin Bayer), small, pin-point bleeding under the skin (petechiae)
- muscle pain, inflammation of the joints, increased muscle tone, cramping, tendon rupture – especially of the large tendon at the back of the ankle (Achilles tendon) (see Section 2: Take special care with Ciprofloxacin Bayer)
- blood or crystals in the urine (see Section 2: Take special care with Ciprofloxacin Bayer), urinary tract inflammation
- excessive sweating
- abnormal levels of a clotting factor (prothromibin) increased levels of the enzyme amylase

Very rare side effects (less than 1 in every 10,000 people are likely to get these):

- a special type of reduced red blood cell count (haemolytic anaemia); a dangerous drop in a type of
  white blood cells (agranulocytosis)
- severe allergic reaction (anaphylactic reaction, anaphylactic shock, serum sickness) which can be fatal (see Section 2: Take special care with Ciprofloxacin Bayer)
- disturbed coordination, unsteady walk (gait disturbance), pressure on the brain (intracranial pressure)
- visual colour distortions
- various skin eruptions or rashes (e.g. the potentially fatal Stevens-Johnson syndrome or toxic epidermal necrolysis)
- muscle weakness, tendon inflammation, worsening of the symptoms of myasthenia gravis (see Section 2: Take special care with Ciprofloxacin Bayer)

Frequency not known (cannot be estimated from the available data)
- troubles associated with the nervous system such as pain, burning, tingling, numbness and/ or weakness in extremities
- severe cardiac rhythm abnormalities, irregular heart beat (Torsades de Pointes)

5. HOW TO STORE CIPROFLOXACIN BAYER

[To be completed nationally]

Keep out of the reach and sight of children.

Do not use Ciprofloxacin Bayer after the expiry date which is stated on the carton after "EXP": The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ciprofloxacin Bayer contains

[To be completed nationally]

What Ciprofloxacin Bayer looks like and contents of the pack

Solution for infusion
[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria:	Ciproxin, Ciprofloxacine « BAYER »
Bulgaria:	Ciprobay
Czech Republic	Ciprobay
France:	Ciflox
Germany:	Ciprobay; Ciprofloxacin ANTIBAC; Ciprofloxacin BAYER; Ciprofloxacin VITAL
Greece:	Ciproxin
Hungary:	Ciprobay
Ireland:	Ciproxin
Italy:	Ciproxin
Malta:	Ciproxin
Netherlands:	Ciproxin
Poland:	Ciprobay
Portugal:	Ciproxina
Romania:	Ciprobay
Slovak Republic:	Ciprobay
Slovenia:	Ciprobay
United Kingdom:	Ciproxin

This leaflet was last approved in {MM/YYYY}

[To be completed nationally]

Advice/medical education

Antibiotics are used to cure bacterial infections. They are ineffective against viral infections.
If your doctor has prescribed antibiotics, you need them precisely for your current illness.
Despite antibiotics, some bacteria may survive or grow. This phenomenon is called resistance: some antibiotic treatments become ineffective.
Misuse of antibiotics increases resistance. You may even help bacteria become resistant and therefore delay your cure or decrease antibiotic efficacy if you do not respect appropriate:
- dosage
- schedules
- duration of treatment

Consequently, to preserve the efficacy of this drug:
1 - Use antibiotics only when prescribed.
2 - Strictly follow the prescription.
3 - Do not re-use an antibiotic without medical prescription, even if you want to treat a similar illness.
4 - Never give your antibiotic to another person; maybe it is not adapted to her/his illness.
5 - After completion of treatment, return all unused drugs to your chemist's shop to ensure they will be disposed of correctly

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The following information is intended for medical or healthcare professionals only

Ciprofloxacin Bayer should be administered by intravenous infusion. For children, the infusion duration is 60 minutes. In adult patients, infusion time is 60 minutes for 400 mg Ciprofloxacin Bayer and 30 minutes for 200 mg Ciprofloxacin Bayer. Slow infusion into a large vein will minimise patient discomfort and reduce the risk of venous irritation. The infusion solution can be infused either directly or after mixing with other compatible infusion solutions.

Unless compatibility with other infusion solutions/drugs has been confirmed, the infusion solution must always be administered separately. The visual signs of incompatibility are e.g. precipitation, clouding, and discolouration.

Incompatibility appears with all infusion solutions/drugs that are physically or chemically unstable at the pH of the solution (e.g. penicillin, heparin solutions), especially in combination with solutions adjusted to an alkaline pH (pH of the ciprofloxacin infusion solutions: 3.9-4.5).

After intravenous initiation of treatment, the treatment can be continued orally as well.