Annex I

List of the names, pharmaceutical forms, strengths of the veterinary medicinal product, animal species, withdrawal period, marketing authorisation holders in the Member States

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Withdrawal periods
Belgium	BAYER SA-NV J.E. Mommaertslaan 14 1831 Diegem (Machelen) BELGIUM	Baytril 10% orale oplossing	Enrofloxacin	100 mg/ml	oral solution	Chickens and turkeys	3 days Not to be used in chicken producing eggs intended for human consumption
Bulgaria	Bayer Animal Health GmbH 51368 Leverkusen GERMANY	Baytril 10% oral solution	Enrofloxacin	100 mg/ml	oral solution	Chickens and turkeys	Chickens: 3 days Turkeys: 3 days
Cyprus	Bayer Animal Health GmbH 51368 Leverkusen GERMANY	Baytril oral solution 10%	Enrofloxacin	100 mg/ml	oral solution	Broiler chickens, breeders, and turkeys	3 days
Denmark	Bayer Animal Health GmBH 51368 Leverkusen GERMANY	Baytril Vet. Oral opløsning	Enrofloxacin	100 mg/ml	oral solution	Poultry, non egglayers	3 days
France	Bayer Sante 220 Avenue De La Recherche 59120 Loos FRANCE	Baytril 10 % Solution Buvable	Enrofloxacin	100 mg/ml	oral solution	Chickens and turkeys	4 days Not for use in birds producing eggs for human consumption
Germany	Bayer Vital GmbH 51368 Leverkusen GERMANY	Baytril 10%	Enrofloxacin	100 mg/ml	oral solution	Chickens and turkeys	Chickens: 3 days Not for use in laying hens Turkeys: 3 days Not for use in laying turkey hens
Greece	Bayer Animal Health GmbH 51368 Leverkusen GERMANY	Baytril 10% oral solution	Enrofloxacin	100 mg/ml	oral solution	Chickens (broiler, pullet) and turkeys	3 days Not to be used in hens producing eggs for human consumption

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Withdrawal periods
Hungary	Bayer Hungária Kft. Alkotás u. 50. 1123 Budapest HUNGARY	Baytril 10 % belsőleges oldat	Enrofloxacin	100 mg/ml	oral solution	Chickens and turkeys	3 days Not for use in laying birds whose eggs are intended for human consumption
Ireland	Bayer Limited Animal Health Division The Atrium Blackthorn Road Dublin 18 IRELAND	Bayer 10% Oral Solution	Enrofloxacin	100 mg/ml	oral solution	Chickens and turkeys	Birds must not be slaughtered for human consumption during treatment. Chickens must not be slaughtered for human consumption until 3 days after the last treatment. Turkeys must not be slaughtered for human consumption until 3 days after the last treatment
Italy	Bayer S.p.a. Viale Certosa 130 I-20156 Milan ITALY	Baytril 10% OL Oral solution	Enrofloxacin	100 mg/ml	oral solution	Chickens (excluding laying hens), turkeys and rabbits	Chicken and turkey: 3 days Rabbit: 15 days Do not administer to animals producing eggs for human consumption
Italy	Bayer S.p.a. Viale Certosa 130 I-20156 Milan ITALY	Baytril 10% Oral solution	Enrofloxacin	100 mg/ml	oral solution	Chickens (excluding laying hens) and turkeys	3 days Do not administer to animals producing eggs for human consumption
Netherlands	Bayer B.V. Animal Health Division Energieweg 1 3641 RT Mijdrecht THE NETHERLANDS	Baytril 10% Orale Oplossing voor kippen kalkoenen	Enrofloxacin	100 mg/ml	oral solution	Chickens and turkeys	Chickens: 3 days Turkeys: 4 days

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Withdrawal periods
Portugal	BAYER PORTUGAL, SA Rua Quinta do Pinheiro, 5 2794-003 Carnaxide PORTUGAL	BAYTRIL 10% SOLUÇÃO ORAL	Enrofloxacin	100 mg/ml	oral solution	Poultry (chickens, turkeys)	Chicken: 7 days Turkey: 10 days Do not administer to laying birds producing eggs for human consumption
Romania	BAYER HEALTH CARE AG 51368 Leverkusen GERMANY	Baytril 10%	Enrofloxacin	100 mg/ml	oral solution	Chickens and turkeys	Chickens, turkeys: 3 days Do not use in poultry producing eggs for human consumption
Slovenia	Bayer d.o.o. Bravničarjeva 13 Ljubljana SLOVENIA	BAYTRIL 10 %	Enrofloxacin	100 mg/ml	oral solution	Chickens and turkeys	Chickens: 3 days Turkeys: 3 days
Sweden	Bayer Animal Health GmbH 51368 Leverkusen GERMANY	Baytril® vet.	Enrofloxacin	100 mg/ml	oral solution	Poultry	3 days Do not use in birds producing eggs for human consumption
United Kingdom	Bayer plc Animal Health Division Bayer House Strawberry Hill Newbury Berkshire RG14 1JA UNITED KINGDOM	Baytril 10% Oral Solution	Enrofloxacin	100 mg/ml	oral solution	Poultry (specifically broiler chickens, broiler breeders and pullets being reared as layers) and turkeys	Do not administer to layer replacement birds within 14 days of coming into lay. Chickens: 8 days Not for use in birds producing eggs for human consumption Turkeys: 8 days

Annex II

Scientific conclusions and grounds for amendment of the summary of product characteristics, labelling and package leaflet

Overall summary of the scientific evaluation of Baytril 10% oral solution and associated names (see annex I)

1. Introduction

Baytril 10% oral solution and associated names contain 100 mg enrofloxacin per ml oral solution for use in drinking water. Baytril 10% oral solution and associated names are veterinary medicinal products authorised for use the target species chickens, turkeys and rabbits for treatment of the respiratory tract and of the digestive tract infections caused by identified bacteria susceptible to enrofloxacin.

On 15 October 2010, the United Kingdom sent a referral notification under Article 34(1) of Directive 2001/82/EC, as amended, to the CVMP/European Medicines Agency for Baytril 10% oral solution and associated names. The United Kingdom referred the issue due to divergent national decisions having been taken by EU countries resulting in discrepancies in the product information for Baytril 10% oral solution and associated names.

The main areas of disharmony in the existing SPCs relate to:

- Target species;
- Indications;
- Posology;
- Withdrawal period;
- User safety warnings;
- Shelf life.

2. Discussion of data available

2.1. Target species, indications and posology

Chickens and turkeys

The marketing authorisation holders confirmed that no marketing authorisation for the product relating to use in chickens or turkeys has been withdrawn, refused, revoked or suspended in any Member State.

Not all indications were included in the product information for all Member States. The marketing authorisation holders agreed to delete the following indications from the product information either due to paucity of supporting data and/or because the indications were not consistent with responsible use on fluoroquinolones: *Salmonella*, *Streptococcus* spp, *Staphylococcus* spp, *Klebsiella*, *Erysipelothrix rhusiopathae*.

Satisfactory data have been submitted to support the use of enrofloxacin at the proposed harmonised dose rate to treat *Avibacterium paragallinarum, Pasteurella multocida, Mycoplasma gallisepticum and Mycoplasma synoviae* in chickens; *Mycoplasma gallisepticum, Mycoplasma synoviae* and *Pasteurella multocida* in turkeys.

Although most Member States had a dose rate of 10 mg/kg for chickens and turkeys, it varied between from 2.5 mg/kg bodyweight to 10 mg/kg bodyweight for duration between 3 to 10 days. From the data submitted however, it is not possible to determine the optimal dose rate for treatment of *Escherichia coli* in either chickens or turkeys. In chickens, the EU studies submitted are approximately 25 years old, involve experimental infections only and were conducted when the Minimum Inhibitory

Concentration (MIC) of *E. coli* was significantly lower than the MIC of *E. coli* today. In studies where the dose could be calculated in mg/kg, although a dose of approximately 10 mg/kg bodyweight was effective as metaphylaxis it appeared that a higher dose was more effective for treatment of *E. coli*. The results of the additional studies submitted for turkeys generally supported the proposed dose rate of 10 mg/kg bodyweight. However, as there are limited data available for treatment of *E. coli* in this minor species, and extrapolation is made from the data provided for chickens, some concerns still remain. The marketing authorisation holders provided a basic PK/PD analysis for enrofloxacin/*E. coli* but this was equivocally supportive of the 10 mg/kg bodyweight dose rate and also suggested that a higher dose might be preferable.

There are not enough data to either determine the optimum dose rate for treatment or to propose an alternative dose rate for poultry, and new studies are required. However, it has to be considered that as *E coli* from poultry are often resistant to first line antimicrobials, fluoroquinolones are recognised as veterinary critically important antimicrobials in the treatment of colibacillosis septicaemia and chronic respiratory disease in this species and it is important to maintain this indication on the SPC. Therefore, and considering the context of this Article 34 referral which is to harmonise the SPCs, CVMP proposed to harmonise to the highest dose rate of enrofloxacin of 10 mg/kg for 3-5 days in both chickens and turkeys, which is also that approved in the majority of Member States. In doing this, CVMP recognises that an effective treatment should be kept available for *E. coli*, but at a future date new data will have to be generated to optimise the dose regimen for all enrofloxacin products administered orally to poultry.

Rabbits

Rabbits were included as a target species in the product information for Italy, only. The marketing authorisation holders confirmed that no marketing authorisation for the product relating to use in rabbits has been withdrawn, refused, revoked or suspended in any Member State.

Regarding the indications for *P. multocida* and *E. coli,* the marketing authorisation holders submitted challenge studies and minimal field data from studies conducted 20 years ago. The challenge studies suggested that a dose of 10 mg/kg bodyweight would be more effective than the proposed 5 mg/kg bodyweight, especially when treating acute cases. In addition, because of the concern that underdosing might encourage the development of antimicrobial resistance, the CVMP agreed to accept an increase in the dose to 10 mg/kg bodyweight during 5 days for this species in order to maintain this minor species in the product information. This is also consistent with the dose for this species/indication stated in the SPC for other comparable EU authorised products.

However, it was acknowledged that the data supporting the increased dose regimen are weak, and therefore a condition should be imposed to the marketing authorisations requiring new data to substantiate the dose regimen for this species.

Since only MIC and minimal field data relating to a mixed infection are provided for the indication of *Bordetella*, this indication should not be included on the product information.

Target animal safety

Risks of use of this product have been illustrated in chickens and turkeys by two comprehensive and recent references. Doses up to 100 mg/kg bodyweight during 5 days or 30 mg/kg bodyweight for 3 weeks were clinically well tolerated in broilers. At doses ≥ 50 mg/kg bodyweight/day administered for 5 days there was histological evidence of a detrimental effect on articular cartilage in broilers, but leg lesions were only clinically apparent in chickens and turkeys at doses > 100 mg/kg administered for ≥ 5 days. The references concluded that administration of the proposed dose rate was safe for the proposed dose duration.

Baytril 10% oral solution at a dose rate of 100 ppm (approximately 10 mg/kg) for 6 days and repeating after a 3 day interval was shown to be safe to use in rabbits aged 30 days, in does at mating and 15 days after mating and when does were lactating. In addition, data from the challenge studies provide evidence that a dose of 10 mg/kg bodyweight for 5 days will be tolerated in rabbits.

There is no evidence of chondrotoxicity in chickens, turkeys or rabbits from Periodic Safety Update Reports over the last 10 years.

Antimicrobial resistance

Concerns were raised by CVMP regarding references highlighting emergence of resistant strains of *M. synoviae* both under experimental conditions (Le Carrou et al[1], 2006) and from commercial poultry in the Netherlands (Landman[2], 2008). However evidence of widespread resistance in the European Union or lack of efficacy of the dose in the treatment of mycoplasmosis is difficult to find.

According to the references submitted by the marketing authorisation holders, resistance rates in *E. coli* from chickens and turkeys are reported as low. However according to the EFSA/ECDC report[3] (2012) resistance to ciprofloxacin in indicator *E. coli* isolates taken from chickens is described as moderate to high at a rate of 47%, although in this report, the resistance rate is based on epidemiological cut-off values for non-pathogenic strains. A recent paper by de Jong et al[4], 2012, quotes data from the European Antimicrobial Susceptibility Surveillance in Animals (EASSA) collected from EU countries. Clinical resistance of *E. coli* in chickens to ciprofloxacin was 1.9% in 1999-2000 and increased through 2002-3 to 5.9% in 2005-6. The paper states that the high values for 2005-6 were due to the high level of resistance in Spain (24%), which was not included in 1999-2000. In this paper, clinical resistance was assessed against the Clinical Laboratory and Standards Institute (CLSI) break-point for ciprofloxacin of ≥ 4 mg/l. Rates of decreased susceptibility of *E. coli* to ciprofloxacin based on an epidemiological cut-off of 0.06 mg/l were 19.3% in 1999-2000 and 33.5% in 2005-6.

The marketing authorisation holders have conducted a basic PK/PD analysis regarding *E. coli*, but no consideration has been given to an antimutant dosing strategy or to the potential to select for resistant food-borne organisms of significance to public health (*Campylobacter, Salmonella*).

Some concerns remain in relation to the dosing regimens for all species, and whether they are optimal in terms of minimising the risk for development of antimicrobial resistance.

Environmental Risk Assessment

The risks for the environment have been assessed previously for a dose of 10 mg/kg bodyweight for 10 consecutive days in broiler chickens. Calculations in broiler chickens produce the highest exposure of the environment (PEC_{soil} 887 µg/kg). Provided this PEC_{soil} is not exceeded, exposure of the environment to enrofloxacin will not increase and the product is not expected to pose a risk for the environment. The exposure of the environment from the use of the product in chickens (PEC_{soil} 887 µg/kg) is greater than the exposure from the treatment of rabbits at the new proposed dose rate of 10 mg/kg during 5 days (PEC_{soil} 361 µg/kg). In this situation, as the rabbit is a minor species, the assessment for broilers covers the use of the product in rabbits and the risk assessment can stop at Phase I.

[1] Le Carrou et al., 2006. Persistence of Mycoplasma synoviae in hens after two enrofloxacin treatments and detection of mutations in the parC gene. Vet. Res., 37, 415-154.
[2] Landman et al., 2008. In vitro antibiotic susceptibility of Dutch Mycoplasma synoviae field isolates originating from joint lesions and the respiratory tract of commercial poultry. Avian Path., 37, 415-420.
[3] European Food Safety Authority and European Centre for Disease Prevention and Control; The European Union Summary Report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2010. EFSA Journal 2012; 10(3):2598 [233 pp.] doi:10.2903/j.efsa.2012.2598. Available online at www.efsa.europa.eu/efsajournal
[4] de Jong A, Stephan B, Silley P.(2012).Fluoroquinolone resistance in E coli and Salmonella from healthy livestock and poultry in the EU. Journal of Applied Microbiology, 112: 239-245.

2.2. Withdrawal periods

The marketing authorisation holders have not provided sufficient residues depletion data to allow a scientifically determined withdrawal period to be set for either turkeys or rabbits. The data provided to show the rate of residue depletion in chickens were also not to current standards, but they were considered to be adequate, for the purposes of this procedure, to set a 3-day meat withdrawal period for chickens. This study was conducted using two breeds of chickens, one fast growing and one slower growing, which together cover the range of chickens used for food in Europe. The first time point at which all residues were below their respective maximum residue limits in the slower-growing birds was at 3 days after final treatment, one day after the faster-growing birds. This study was also considered to be adequate to be used to set a 3-day withdrawal period for turkeys, by extrapolation from the chicken data. Therefore, a 3-day meat withdrawal period can be adopted for the harmonised product information for both chickens and turkeys. This is consistent with the withdrawal period that has been in force in the majority of Member States, in which the product has been authorised for many years.

There are not sufficient data available to set a scientifically-derived withdrawal period in rabbits, but the limited data available show that the first time point at which all residues were below the MRLs set by the CVMP was at 2 days after the final treatment. Because the data available was inconclusive, and furthermore because the CVMP agreed that the dose for this species should be increased, as a pragmatic approach it is proposed to retain the current 15-day withdrawal period as this will ensure consumer safety, considering the rapid depletion shown in poultry and rabbits.

Enrofloxacin does not have a maximum residue limit for eggs, and therefore birds laying eggs for human consumption must not be treated with Baytril 10% oral solution and its associated names.

2.3. User risk assessment

The marketing authorisation holders have provided a user risk assessment which, although not fully compliant with the current guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1)[5], does cover the main risks associated with this product, and can be used to determine user safety warnings to appear on the product information. The hazards associated with use of the product are developmental reactions which will not become apparent at the low accidental exposure levels assumed.

2.4. Shelf life

The product shows good physical and chemical stability over a 48 month storage period, and the data support the proposed shelf life of 48 months without any special storage precautions

The data package supports an in-use shelf life of 12 weeks and an in-use shelf life after dilution of 24 hours.

3. Benefit-risk assessment

The product has been shown to be efficacious in the treatment of *E. coli*, *Avibacterium paragallinarum, Pasteurella multocida, Mycoplasma gallisepticum and Mycoplasma synoviae* in chickens; *E. coli, Mycoplasma gallisepticum, Mycoplasma synoviae* and *Pasteurella multocida* in turkeys.

[5] CVMP guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500077971.pdf

Although some concern remains that the dose regimen may not be optimal for the treatment of *E. coli*, and with regard to limiting the risk for the development of antimicrobial resistance, it is recognised that enrofloxacin is critically important for the treatment of colibacillosis in poultry. Therefore, and taking account of the scope of this Article 34 referral, the indication can be retained in the harmonised SPC.

Regarding the indications for *P. multocida* and *E. coli* for rabbits, it was agreed that with an increase to the dose, the benefit-risk for this minor species would remain positive, however a condition should be imposed to the marketing authorisations requiring new data to substantiate the dose regimen for this species.

The product is well tolerated by the target species, and presents a low risk for users and the environment when used in accordance with the harmonised warnings included in the SPC. Satisfactory withdrawal periods have been set to provide assurance of consumer safety.

The proposed SPC contains the warnings regarding prudent use of fluoroquinolones in food producing animals in line with the CVMP reflection paper 2006[6]. By limiting the use of the product, these warnings are intended to minimise the potential impact on human and animal health from antimicrobial resistance.

The CVMP has proposed further amendments to the warnings regarding resistance in section 4.5 of the SPC (Special precautions for use). A warning in relation to the potential effects of overdosing of fluoroquinolones on cartilage during the growth phase is included in section 4.10 of the SPC (Overdose). User safety warnings are included on the product information.

The veterinary medicinal product has been appropriately formulated and the harmonised shelf life is appropriate to ensure that quality is maintained during use.

The overall benefit-risk balance for this product is deemed positive subject to the recommended changes in the product information (see annex III) and subject to condition affecting the marketing authorisations (see annex IV).

Grounds for amendment of the summary of product characteristics, labelling and package leaflet

Whereas

- the CVMP considered the scope of the referral was the harmonisation of the summary of products characteristics, labelling and package leaflet;
- the CVMP reviewed the summary of products characteristics, labelling and package leaflet proposed by the marketing authorisation holders and considered all the overall submitted data;

the CVMP 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 Baytril 10% oral solution and associated names (see annex I).

[6] CVMP Reflection paper on the use of fluoroquinolones in food- producing animals – Precautions for use in the SPC regarding prudent use guidance (EMEA/CVMP/416168/2006) - http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500005173.pdf

Annex III

Summary of product characteristics, labelling and package leaflet

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

"Product name" (to be completed nationally)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of *"Product name"* (*to be completed nationally*) contains:

Active substance:

Enrofloxacin 100 mg;

Excipient(s):

Benzyl alcohol 14 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for use in drinking water.
Clear yellowish solution.

4. CLINICAL PARTICULARS

4.1 Target species

Chicken, turkey and rabbit.

4.2 Indications for use, specifying the target species

Treatment of the respiratory tract and of the digestive tract infections caused by the following bacteria susceptible to enrofloxacin:

Chickens
Mycoplasma gallisepticum,
Mycoplasma synoviae,
Avibacterium paragallinarum,
Pasteurella multocida,
Escherichia coli.

Turkeys
Mycoplasma gallisepticum,
Mycoplasma synoviae,
Pasteurella multocida,
Escherichia coli.

Rabbits
For the treatment infectious diseases due to *Pasteurella multocida* and bacterial enteritis due to infection with *E. coli.*

Enrofloxacin should be used where clinical experience, supported where possible by sensitivity testing of the causal organism, indicates enrofloxacin as the active substance of choice.

4.3 Contraindications

Do not use for prophylaxis.
Do not use when resistance / cross-resistance to (fluoro)quinolones is known to occur.
Do not use in the case of known hypersensitivity to the active substance, other (fluoro)quinolones or to any of the excipients.

4.4 Special warnings for each target species

None known.

4.5 Special precautions for use

Special precautions for use in animals

Official and local antimicrobial policies should be taken into account when the product is used.

Fluoroquinolones should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials.
Since enrofloxacin was first authorised for use in poultry, there has been widespread reduction in susceptibility of *E. coli* to fluoroquinolones and emergence of resistant organisms. Resistance has also been reported in *Mycoplasma synoviae* in the EU.

Whenever possible fluoroquinolones should only be used based on susceptibility testing.

Use of the product deviating from the instructions given by in the SPC may increase the prevalence of bacteria resistant to the fluoroquinolones and may decrease the effectiveness of treatment with other fluoroquinolones due to the potential for cross-resistance.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

Those with known hypersensitivity to (fluoro)quinolones should avoid contact with this product.
Avoid contact with skin and eyes.
Rinse any splashes from skin or eyes immediately with water.
Wash hands and exposed skin after use.
Do not eat, drink or smoke whilst using the product.

4.6 Adverse reactions (frequency and seriousness)

None known.

4.7 Use during pregnancy, lactation or lay

Do not use in laying hens producing eggs for human consumption.
Do not administer to layer replacement birds within 14 days of coming into lay.

4.8 Interaction with other medicinal products and other forms of interaction

In vitro, an antagonism was shown, when combining fluoroquinolones with bacteriostatic antimicrobial agents such as macrolides or tetracyclines and phenicols. The simultaneous application of substances containing aluminium or magnesium can impair the absorption of enrofloxacin.

4.9 Amounts to be administered and administration route

Chickens and turkeys

10 mg enrofloxacin/kg bodyweight per day for 3–5 consecutive days.

Treatment for 3–5 consecutive days; for 5 consecutive days in mixed infections and chronic progressive forms. If no clinical improvement is achieved within 2–3 days, alternative antimicrobial therapy should be considered based on susceptibility testing.

Via the drinking water. Always make sure that the entire dose offered has been consumed. The medicated water should be made up fresh each day just before it is offered to the animals. The drinking water must be medicated throughout the treatment period, and no other water source should be available. Determine the bodyweight of the birds as accurately as possible in order to avoid underdosing.

Use only fresh pre-solutions, prepared every day before start of treatment. Pumping systems should be checked constantly to assure proper medication. Empty the water system and fill it with medicated water before starting the treatment.

Calculate the daily quantity (ml) of *"Product name"* (*to be completed nationally*) required for treatment period as follows:

Total number of birds x Average body weight in kg x 0.1 = Total volume (ml) per day

"Product name" (to be completed nationally) may be put directly into the header tank or introduced via a water proportioner pump.

Rabbits

10 mg/kg bodyweight per day for 5 consecutive days.

Calculate the daily quantity (ml) of *"Product name"* (*to be completed nationally*) required for treatment period as follows:

Total number of rabbits x Average body weight in kg x 0.1 = Total volume (ml) per day

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

No adverse clinical symptoms were observed in chickens and turkeys treated respectively with doses up to 10 and 6 times higher than the therapy dose.
The use of fluoroquinolones during the growth phase combined with a marked and prolonged increase in the intake of drinking water, and hence active ingredient, possibly due to high temperatures, may potentially be associated with damage of the articular cartilage.

4.11 Withdrawal period(s)

Chickens: Meat and offal: 3 days.
Turkeys: Meat and offal: 3 days.
Rabbits: Meat and offal: 15 days.

Not authorised for use in birds producing eggs for human consumption.
Do not administer to layer replacement birds within 14 days of coming into lay.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: quinolone and quinoxaline antibacterials, fluoroquinolones.
ATCvet code: QJ01MA90.

5.1 Pharmacodynamic properties

Mode of action

Two enzymes essential in DNA replication and transcription, DNA gyrase and topoisomerase IV, have been identified as the molecular targets of fluoroquinolones. They modulate the topological state of DNA through cleaving and resealing reactions. Initially, both strands of the DNA double helix are cleaved. Then, a distant segment of DNA is passed through this break before the strands are resealed. Target inhibition is caused by non-covalent binding of fluoroquinolone molecules to an intermediate state in this sequence of reactions, in which DNA is cleaved, but both strands are retained covalently attached to the enzymes. Replication forks and translational complexes cannot proceed beyond such enzyme-DNA-fluoroquinolone complexes, and inhibition of DNA and mRNA synthesis triggers events resulting in a rapid, drug concentration-dependent killing of pathogenic bacteria.

Antibacterial spectrum

Enrofloxacin is active against many Gram-negative bacteria, against Gram-positive bacteria and *Mycoplasma* spp.
In vitro susceptibility has been shown in strains of (i) Gram-negative species such as *Escherichia coli, Pasteurella multocida* and *Avibacterium (Haemophilus) paragallinarum* and (ii) *Mycoplasma gallisepticum* and *Mycoplasma synoviae*. (See section 4.5)

Types and mechanisms of resistance

Resistance to fluoroquinolones has been reported to arise from five sources, (i) point mutations in the genes encoding for DNA gyrase and/or topoisomerase IV leading to alterations of the respective enzyme, (ii) alterations of drug permeability in Gram-negative bacteria, (iii) efflux mechanisms, (iv) plasmid mediated resistance and (v) gyrase protecting proteins. All mechanisms lead to a reduced susceptibility of the bacteria to fluoroquinolones. Cross-resistance within the fluoroquinolone class of antimicrobials is common.

5.2 Pharmacokinetic particulars

Enrofloxacin administered via drinking water to poultry is rapidly and very well absorbed with a bioavailability of approx. 90 %. Maximum plasma concentrations of 2 mg/L are reached within 1.5 hours after a single bolus dose rate of 10 mg/kg body weight with a total systemic availability of 14.4 mg·hr/L. Enrofloxacin is eliminated from the body with a total body clearance of 10.3 mL/min·kg. If dosed as continuous drinking water medication (multiple dosing) steady-state concentrations of 0.5 mg (turkeys) to 0.8 mg (chicken) enrofloxacin per litre are achieved. A high mean volume of distribution (5 L/kg) indicates good tissue penetration of enrofloxacin. Concentrations in target tissues like lungs, liver, kidney, intestine and muscle tissue, exceed plasma concentrations by far. In poultry enrofloxacin is poorly metabolized to its active metabolite ciprofloxacin (approximately 5 %). Enrofloxacin is eliminated from the body at a half-life of 6 hours. Protein binding in poultry is approximately 25 %.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol

Potassium hydroxide
Purified water.

6.2 Incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 4 years.
Shelf life after first opening the immediate packaging: 12 weeks.
Shelf life after dilution or reconstitution according to directions: 24 hours.

6.4 Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

6.5 Nature and composition of immediate packaging

100 ml, 500 ml and 1,000 ml high density polyethylene (HDPE) bottles with an HDPE insert and a polypropylene screw closure.

5,000 ml HDPE canister with an aluminium/HDPE seal and an HDPE screw closure.

The containers are provided with a graduated polypropylene measuring cup.

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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
<Date of first authorisation:> <{DD/MM/YYYY}><{DD month YYYY}>.
<Date of last renewal:> <{DD/MM/YYYY}><{DD month YYYY}>.

10. DATE OF REVISION OF THE TEXT

To be completed nationally
{MM/YYYY}

PROHIBITION OF SALE, SUPPLY AND/OR USE

To be completed nationally

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Card box (100 ml bottle)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

"Product name" (*to be completed nationally*)

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

One ml of *"Product name"* (*to be completed nationally*) contains:

Active substance:

Enrofloxacin 100 mg

Excipient(s):

Benzyl alcohol 14 mg.

3. PHARMACEUTICAL FORM

Solution for use in drinking water.
Clear yellowish solution.

4. PACKAGE SIZE

100 ml

5. TARGET SPECIES

Chicken, turkey and rabbit.

6. INDICATION(S)

Please read package leaflet carefully before use.

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Via the drinking water. Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Withdrawal period:
Chickens: Meat and offal: 3 days.

Turkeys: Meat and offal: 3 days.
Rabbits: Meat and offal: 15 days.

Not authorised for use in birds producing eggs for human consumption.
Do not administer to layer replacement birds within 14 days of coming into lay.

9. SPECIAL WARNING(S), IF NECESSARY

User safety warnings:

- Those with known hypersensitivity to (fluoro)quinolones should avoid contact with this product.
- Avoid contact with skin and eyes.
- Rinse any splashes from skin or eyes immediately with water.
- Wash hands and exposed skin after use.
- Do not eat, drink or smoke whilst using the product.

Read the package leaflet before use.

10. EXPIRY DATE

EXP: {month/year}
Following withdrawal of the first dose use the product within 12 weeks.
Discard unused material.
Medicated water should be made up on a daily basis. Any medicated water remaining after 24 hours after preparation must be discarded.
The date of the first withdrawal should be recorded on the label.

11. SPECIAL STORAGE CONDITIONS

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally.

{Name and address}
<{tel}>

<{fax}>
<{e-mail}>

16. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

17. MANUFACTURER'S BATCH NUMBER

Lot: {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

Bottle or canister

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

"Product name" (*to be completed nationally*)

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

One ml of *"Product name"* (*to be completed nationally*) contains:

Active substance:

Enrofloxacin 100 mg

Excipient(s):

Benzyl alcohol 14 mg.

3. PHARMACEUTICAL FORM

Solution for use in drinking water.
Clear yellowish solution.

4. PACKAGE SIZE

100 ml
500 ml
1,000 ml
5,000 ml

5. TARGET SPECIES

Chicken, turkey and rabbit.

6. INDICATION(S)

Please read package leaflet carefully before use.

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Via the drinking water. Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Withdrawal period:
Chickens: Meat and offal: 3 days.
Turkeys: Meat and offal: 3 days.
Rabbits: Meat and offal: 15 days.

Not authorised for use in birds producing eggs for human consumption.
Do not administer to layer replacement birds within 14 days of coming into lay.

9. SPECIAL WARNING(S), IF NECESSARY

User safety warnings:

- Those with known hypersensitivity to (fluoro)quinolones should avoid contact with this product.
- Avoid contact with skin and eyes.
- Rinse any splashes from skin or eyes immediately with water.
- Wash hands and exposed skin after use.
- Do not eat, drink or smoke whilst using the product.

Read the package leaflet before use.

10. EXPIRY DATE

EXP: {month/year}
Following withdrawal of the first dose use the product within 12 weeks.
Discard unused material.
Medicated water should be made up on a daily basis. Any medicated water remaining after 24 hours after preparation must be discarded.
The date of the first withdrawal should be recorded on the label.

11. SPECIAL STORAGE CONDITIONS

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally.

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

16. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

17. MANUFACTURER'S BATCH NUMBER

Lot: {number}

B. PACKAGE LEAFLET

PACKAGE LEAFLET FOR:
"Product name"
To be completed nationally.

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

To be completed nationally.

<Marketing authorisation holder <and manufacturer responsible for batch release>:

<Manufacturer responsible for batch release:>

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

"Product name" (*to be completed nationally*)

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

One ml of *"Product name"* (*to be completed nationally*) contains:

Active substance:

Enrofloxacin 100 mg;

Excipient(s):

Benzyl alcohol 14 mg.

4. INDICATION(S)

Treatment of the respiratory tract and of the digestive tract infections caused by the following bacteria susceptible to enrofloxacin:

Chickens infected with
Mycoplasma gallisepticum,
Mycoplasma synoviae,
Avibacterium paragallinarum,
Pasteurella multocida,
Escherichia coli;

Turkeys infected with
Mycoplasma gallisepticum,
Mycoplasma synoviae,
Pasteurella multocida,
Escherichia coli.

Rabbits
For the treatment infectious diseases due to *Pasteurella multocida* and bacterial enteritis due to infection with *E. coli.*

Enrofloxacin should be used where clinical experience, supported where possible by sensitivity testing of the causal organism, indicates enrofloxacin as the active substance of choice.

5. CONTRAINDICATIONS

Do not use for prophylaxis.
Do not use when resistance / cross resistance to (fluoro)quinolones is known to occur.
Do not use in the case of known hypersensitivity to the active substance, other (fluoro)quinolones or to any of the excipients.

6. ADVERSE REACTIONS

If you notice any serious effects or other effects not mentioned in this leaflet, please inform your veterinary surgeon.

7. TARGET SPECIES

Chicken, turkey and rabbit.

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

Chickens and turkeys

10 mg enrofloxacin/kg bodyweight per day for 3–5 consecutive days.

Treatment for 3–5 consecutive days; for 5 consecutive days in mixed infections and chronic progressive forms. If no clinical improvement is achieved within 2–3 days, alternative antimicrobial therapy should be considered based on susceptibility testing.

Via the drinking water. Always make sure that the entire dose offered has been consumed. The medicated water should be made up fresh each day just before it is offered to the animals. The drinking water must be medicated throughout the treatment period, and no other water source should be available. Determine the bodyweight of the birds as accurately as possible in order to avoid underdosing.

Use only fresh pre-solutions, prepared every day before start of treatment. Pumping systems should be checked constantly to assure proper medication. Empty the water system and fill it with medicated water before starting the treatment.

Calculate the daily quantity (ml) of *"Product name"* (*to be completed nationally*) required for treatment period as follows:

Total number of birds x Average body weight in kg x 0.1 = Total volume (ml) per day

"Product name" (to be completed nationally) may be put directly into the header tank or introduced via a water proportioner pump.

Rabbits

10 mg/kg bodyweight per day for 5 consecutive days.

Calculate the daily quantity (ml) of *"Product name"* (*to be completed nationally*) required for treatment period as follows:

Total number of rabbits x Average body weight in kg x 0.1 = Total volume (ml) per day

9. ADVICE ON CORRECT ADMINISTRATION

For chickens and turkeys, please refer to section 8.

10. WITHDRAWAL PERIOD

Chickens: Meat and offal: 3 days.
Turkeys: Meat and offal: 3 days.
Rabbits: Meat and offal: 15 days.

Not authorised for use in birds producing eggs for human consumption.
Do not administer to layer replacement birds within 14 days of coming into lay.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
Do not use this veterinary medicinal product after the expiry date which is stated on the packaging.
Shelf-life after first opening the immediate packaging: 12 weeks.
The date of the first withdrawal should be recorded on the label.

12. SPECIAL WARNING(S)

Official and local antimicrobial policies should be taken into account when the product is used.
Fluoroquinolones should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials.
Since enrofloxacin was first authorised for use in poultry, there has been widespread reduction in susceptibility of *E. coli* to fluoroquinolones and emergence of resistant organisms. Resistance has also been reported in *Mycoplasma synoviae* in the EU.
Whenever possible fluoroquinolones should only be used based on susceptibility testing.
Use of the product deviating from the instructions given may increase the prevalence of bacteria resistant to the fluoroquinolones and may decrease the effectiveness of treatment with other fluoroquinolones due to the potential for cross-resistance.
Use of fluoroquinolones during the growth phase combined with a marked and prolonged increase in the intake of drinking water, and hence active ingredient, possibly due to high temperatures, may potentially be associated with damage of the articular cartilage.
No adverse clinical symptoms were observed in chickens and turkeys treated respectively with doses up to 10 and 6 times higher than the therapy dose.
In vitro, an antagonism was shown, when combining fluoroquinolones with bacteriostatic antimicrobial agents such as macrolides or tetracyclines and phenicols. The simultaneous application of substances containing aluminium or magnesium can impair the absorption of enrofloxacin.
No adverse clinical symptoms were observed in chickens and turkeys treated respectively with doses up to 10 and 6 times higher than the therapy dose.

User safety warnings:
- Those with known hypersensitivity to (fluoro)quinolones should avoid contact with this product.
- Avoid contact with skin and eyes.

- Rinse any splashes from skin or eyes immediately with water.
- Wash hands and exposed skin after use.
- Do not eat, drink or smoke whilst using the product.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIAL, IF ANY

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

To be completed nationally.

15. OTHER INFORMATION

Bottles of 100, 500 and 1,000 ml or canister of 5,000 ml.

Not all pack sizes may be marketed.

Annex IV

Condition of the marketing authorisations

The National Competent Authorities shall ensure that the following condition is fulfilled by the marketing authorisation holders:

- The marketing authorisation holders should substantiate the dosing regimen in rabbits taking into account the current MIC distribution for the target pathogens, the variability in pharmacokinetics resulting from administration of enrofloxacin via the drinking water to groups of rabbits under field conditions and with the goal to ensure sustainable effective treatment.
- Residue depletion studies should be provided for any proposed new dosage regimen. A shorter or lower dose regimen than the current 10 mg/kg for 5 days needs to be substantiated by new clinical data.

The results of those studies should be provided to the relevant Authorities for assessment not later than 18 months after the Commission Decision on this referral procedure.