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 EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Austria	AstraZeneca Österreich GmbH, Schwarzenbergplatz 7 A-1037 Wien Austria	Optinem i.v. 500 mg - Trockenstechampullen	500 mg	Powder for solution for injection or infusion	Intravenous use	500 mg/20ml
Austria	AstraZeneca Österreich GmbH, Schwarzenbergplatz 7 A-1037 Wien Austria	Optinem i.v. 1 g - Trockenstechampullen	1 g	Powder for solution for injection or infusion	Intravenous use	1g /30ml
Belgium	NV AstraZeneca SA Rue Egide Van Ophemstraat 110 1180 Brussel Belgium	Meronem IV 500mg	500 mg	Powder for solution for injection or infusion	Intravenous use	500 mg/20 ml
Belgium	NV AstraZeneca SA Rue Egide Van Ophemstraat 110 1180 Brussel Belgium	Meronem IV 1g	1 g	Powder for solution for injection or infusion	Intravenous use	1g/30 ml
Bulgaria	AstraZeneca UK Limited 600 Capability Green Luton LU1 3LU United Kingdom	Meronem	500 mg	Powder for solution for injection or infusion	Intravenous use	500 mg/20 ml
Bulgaria	AstraZeneca UK Limited 600 Capability Green Luton LU1 3LU United Kingdom	Meronem	1 g	Powder for solution for injection or infusion	Intravenous use	1g/30 ml
Cyprus	AstraZeneca UK Ltd. Silk Road Business Park 1 Macclesfield Cheshire SK10 2NA United Kingdom	MERONEM	500 mg	Powder for solution for injection or infusion	Intravenous use	500 mg/20 ml

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Cyprus	AstraZeneca UK Ltd. Silk Road Business Park 1 Macclesfield Cheshire SK10 2NA United Kingdom	MERONEM	1 g	Powder for solution for injection or infusion	Intravenous use	1g/30 ml
Czech Republic	AstraZeneca UK Ltd. Silk Road Business Park 1 Macclesfield Cheshire SK10 2NA United Kingdom	MERONEM	500 mg	Powder for solution for injection	Intravenous use	500 mg/20 ml
Czech Republic	AstraZeneca UK Ltd. Silk Road Business Park 1 Macclesfield Cheshire SK10 2NA United Kingdom	MERONEM	1 g	Powder for solution for injection	Intravenous use	1g/30 ml
Denmark	AstraZeneca A/S Roskildevej 22 2620 Albertslund Denmark	MERONEM	500 mg	Powder for solution for injection or infusion	Intravenous use	500 mg/20 ml
Denmark	AstraZeneca A/S Roskildevej 22 2620 Albertslund Denmark	MERONEM	1 g	Powder for solution for injection or infusion	Intravenous use	1g/30 ml
Estonia	AstraZeneca UK Limited 15 Stanhope Gate London W1K 1LN United Kingdom	Meronem	500mg	Powder for solution for injection or infusion	Intravenous use	500 mg/10 ml
Estonia	AstraZeneca UK Limited 15 Stanhope Gate London W1K 1LN United Kingdom	Meronem	1g	Powder for solution for injection or infusion	Intravenous use	1g/20 ml

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Finland	AstraZeneca Oy Luomanportti 3 FI-02200 Espoo Finland	Meronem 500mg	500 mg	Powder for solution for injection or infusion	Intravenous use	500 mg/20 ml
Finland	AstraZeneca Oy Luomanportti 3 FI-02200 Espoo Finland	Meronem 1g	1 g	Powder for solution for injection or infusion	Intravenous use	1g/30 ml
France	AstraZeneca 1, Place Renault 92844 RUEIL-MALMAISON Cédex France	MERONEM 500mg poudre pour solution injectable IV	500mg	Powder for solution for injection or infusion	Intravenous use	500 mg/20 ml
France	AstraZeneca 1, Place Renault 92844 RUEIL-MALMAISON Cédex France	MERONEM 1g poudre pour solution injectable IV	1g	Powder for solution for injection or infusion	Intravenous use	1g/30 ml
Germany	AstraZeneca GmbH Tinsdaler Weg 183 22880 Wedel Germany	Meronem 500 mg	500 mg	Powder for solution for injection or infusion	Intravenous use	500 mg/10 ml 5 mg / ml
Germany	AstraZeneca GmbH Tinsdaler Weg 183 22880 Wedel Germany	Meronem 1000 mg	1 g	Powder for solution for injection or infusion	Intravenous use	1g/20 ml 5 mg / ml
Greece	"CANA" SA Pharmaceutical laboratories 446 Irakliou Ave. 14122 Iraklio Attikis Greece	Meronem	500 mg	Powder for solution for injection or infusion	Intravenous use	500 mg/20 ml

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Greece	"CANA" SA Pharmaceutical laboratories 446 Irakliou Ave 14122 Iraklio Attikis Greece	Meronem	1 g	Powder for solution for injection or infusion	Intravenous use	1g/30 ml
Hungary	AstraZeneca Kft. H-2045 Törökbálint Park u. 3. Hungary	Meronem 500mg intravenas injekcio	500mg	Powder for solution for injection or infusion	Intravenous use	500 mg/20 ml
Hungary	AstraZeneca Kft. H-2045 Törökbálint Park u. 3. Hungary	Meronem 1g intravenas injekcio	1g	Powder for solution for injection or infusion	Intravenous use	1g/30 ml
Iceland	AstraZeneca UK Ltd. Alderley Park Macclesfield Cheshire SK10 4TG United Kingdom	Meronem 500 mg stungulyfs-/ innrennslisstofn, lausn.	500mg	Powder for solution for injection or infusion	Intravenous use	500 mg/20 ml
Iceland	AstraZeneca UK Ltd. Alderley Park Macclesfield Cheshire SK10 4TG United Kingdom	Meronem 1 g stungulyfs-/innrennslisstofn, lausn.	1g	Powder for solution for injection or infusion	Intravenous use	1g/30 ml
Ireland	AstraZeneca UK Limited 600 Capability Green Luton Bedfordshire LU1 3LU United Kingdom	Meronem IV 0.5 g powder for solution for injection or infusion.	0.5g	Powder for solution for injection or infusion.	Intravenous use	500 mg/20 ml
Ireland	AstraZeneca UK Limited 600 Capability Green Luton Bedfordshire LU1 3LU United Kingdom	Meronem IV 1 g powder for solution for injection or infusion.	1g	Powder for solution for injection or infusion.	Intravenous use	1g/30 ml

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Italy	AstraZeneca S.p.A. Palazzo Volta Via F. Sforza 20080 Basiglio (MI) Italy	MERREM	500 mg	Powder for solution for injection or infusion	Intravenous use	500 mg
Italy	AstraZeneca S.p.A. Palazzo Volta Via F. Sforza 20080 Basiglio (MI) Italy	MERREM	1 g	Powder for solution for injection or infusion	Intravenous use	1g
Italy	AstraZeneca S.p.A. Palazzo Volta Via F. Sforza 20080 Basiglio (MI) Italy	MERREM	500 mg	Powder and solvent for solution for injection	Intramuscular use	500 mg/2 ml (not marketed)
Italy	AstraZeneca S.p.A. Palazzo Volta Via F. Sforza 20080 Basiglio (MI) Italy	MERREM	250 mg	Powder and solvent for solution for injection or infusion	Intravenous use	250 mg/5 ml (not marketed)
Italy	AstraZeneca S.p.A. Palazzo Volta Via F. Sforza 20080 Basiglio (MI) Italy	MERREM	500 mg	Powder and solvent for solution for injection or infusion	Intravenous use	500 mg/10 ml (not marketed)
Italy	AstraZeneca S.p.A. Palazzo Volta Via F. Sforza 20080 Basiglio (MI) Italy	MERREM	1 g	Powder and solvent for solution for injection or infusion	Intravenous use	1g/20 ml (not marketed)

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Italy	AstraZeneca S.p.A. Palazzo Volta Via F. Sforza 20080 Basiglio (MI) Italy	MERREM	250 mg	Powder and solvent for solution for infusion	Intravenous use	250 mg/100 ml (not marketed)
Italy	AstraZeneca S.p.A. Palazzo Volta Via F. Sforza 20080 Basiglio (MI) Italy	MERREM	500 mg	Powder and solvent for solution for infusion	Intravenous use	500 mg/100 ml (not marketed)
Italy	AstraZeneca S.p.A. Palazzo Volta Via F. Sforza 20080 Basiglio (MI) Italy	MERREM	1 g	Powder and solvent for solution for infusion	Intravenous use	1 g/100 ml (not marketed)
Latvia	AstraZeneca UK Ltd. Silk Road Business Park 1 Macclesfield Cheshire SK10 2NA United Kingdom	Meronem 500mg	500mg	Powder for solution for injection or infusion	Intravenous use	500 mg/20 ml
Latvia	AstraZeneca UK Ltd. Silk Road Business Park 1 Macclesfield Cheshire SK10 2NA United Kingdom	Meronem 1g	1g	Powder for solution for injection or infusion	Intravenous use	1g/30 ml
Lithuania	AstraZeneca UK Ltd. Silk Road Business Park 1 Macclesfield Cheshire SK10 2NA United Kingdom	Meronem IV	500 mg	Powder for solution for injection or infusion	Intravenous use	500 mg/10 ml

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Lithuania	AstraZeneca UK Ltd. Silk Road Business Park 1 Macclesfield Cheshire SK10 2NA United Kingdom	Meronem IV	1 g	Powder for solution for injection or infusion	Intravenous use	1g/20 ml
Luxembourg	NV AstraZeneca SA Rue Egide Van Ophemstraat 110 1180 Brussel Belgium	Meronem IV 500mg	500mg	Powder for solution for injection or infusion	Intravenous use	500 mg/20 ml
Luxembourg	NV AstraZeneca SA Rue Egide Van Ophemstraat 110 1180 Brussel Belgium	Meronem IV 1g	1g	Powder for solution for injection or infusion	Intravenous use	1g/30 ml
Malta	AstraZeneca UK Ltd. Silk Road Business Park 1 Macclesfield Cheshire SK10 2NA United Kingdom	Meronem IV 0.5 g powder for solution for injection or infusion.	0.5g	Powder for solution for injection or infusion	Intravenous use	500 mg/20 ml
Malta	AstraZeneca UK Ltd. Silk Road Business Park 1 Macclesfield Cheshire SK10 2NA United Kingdom	Meronem IV 1 g powder for solution for injection or infusion.	1g	Powder for solution for injection or infusion	Intravenous use	1g/30 ml
Netherlands	AstraZeneca BV at the Louis Pasteurlaan 5 2719 EE, Zoetermeer, Netherlands	Meronem i.v.	250 mg	Powder for solution for injection or infusion	Intravenous use	In the process of being cancelled
Netherlands	AstraZeneca BV at the Louis Pasteurlaan 5 2719 EE, Zoetermeer, Netherlands	Meronem i.v.	500 mg	Powder for solution for injection or infusion	Intravenous use	500 mg/20 ml

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Netherlands	AstraZeneca BV at the Louis Pasteurlaan 5 2719 EE, Zoetermeer, Netherlands	Meronem i.v.	1 g	Powder for solution for injection or infusion	Intravenous use	1g/30 ml
Norway	AstraZeneca AS Hoffsveien 70 B/Postboks 200 Vinderen 0319 OSLO Norway	Meronem	500 mg	Powder for solution for injection or infusion	Intravenous use	500 mg/20 ml
Norway	AstraZeneca AS Hoffsveien 70 B/Postboks 200 Vinderen 0319 OSLO Norway	Meronem	1 g	Powder for solution for injection or infusion	Intravenous use	1g/30 ml
Poland	AstraZeneca UK Ltd. Silk Road Business Park 1 Macclesfield Cheshire SK10 2NA United Kingdom	Meronem	500 mg	Powder for solution for injection	Intravenous use	500 mg/20 ml
Poland	AstraZeneca UK Ltd. Silk Road Business Park 1 Macclesfield Cheshire SK10 2NA United Kingdom	Meronem	1 g	Powder for solution for injection	Intravenous use	1g/30 ml
Portugal	AstraZeneca Produtos Farmacêuticos, Lda. Rua Humberto Madeira, n.º 7, Valejas 2745-663 Barcarena, Portugal	Meronem	500mg	Powder for solution for injection	Intramuscular use	500 mg/2 ml (not marketed)

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Portugal	AstraZeneca Produtos Farmacêuticos, Lda. Rua Humberto Madeira, n.º 7, Valejas 2745-663 Barcarena, Portugal	Meronem	500mg	Powder for solution infusion	Intravenous use	500 mg/20 ml
Portugal	AstraZeneca Produtos Farmacêuticos, Lda. Rua Humberto Madeira, n.º 7, Valejas 2745-663 Barcarena, Portugal	Meronem	1 g	Powder for solution for injection or infusion	Intravenous use	1g/30 ml
Romania	AstraZeneca UK Limited 600 Capability Green Luton Bedfordshire LU1 3LU United Kingdom	Meronem i.v. 500 mg	500 mg	Powder for solution for injection or infusion	Intravenous use	500 mg/20 ml
Romania	AstraZeneca UK Limited 600 Capability Green Luton Bedfordshire LU1 3LU United Kingdom	Meronem i.v. 1g	1g	Powder for solution for injection or infusion	Intravenous use	1g/30 ml
Slovak Republic	AstraZeneca UK Ltd. Silk Road Business Park 1 Macclesfield Cheshire SK10 2NA United Kingdom	Meronem 500mg i.v.	500 mg	Powder for solution for injection or infusion	Intravenous use	500 mg/20 ml
Slovenia	AstraZeneca UK Limited 15 Stanhope Gate London W1K 1LN United Kingdom	Meronem 500mg prasek za raztopino za injiciranje ali infundiranje	500 mg	Powder for solution for injection or infusion	Intravenous use	50mg/ml
Slovenia	AstraZeneca UK Limited 15 Stanhope Gate London W1K 1LN United Kingdom	Meronem 1g prasek za raztopino za injiciranje ali infundiranje	1 g	Powder for solution for injection or infusion	Intravenous use	50mg/ml

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Spain	AstraZeneca Farmacéutica Spain, S.A. C/ Serrano Galvache 56 Edificio Roble 28033 Madrid Spain	Meronem I.V., 500	500 mg	Powder for solution for injection or infusion	Intravenous use	500 mg/20 ml
Spain	AstraZeneca Farmacéutica Spain, S.A. C/ Serrano Galvache 56 Edificio Roble 28033 Madrid Spain	Meronem I.V., 1000	1 g	Powder for solution for injection or infusion	Intravenous use	1g/30 ml
Sweden	AstraZeneca AB 151 85 Södertälje Sweden	Meronem	500 mg	Powder for solution for injection or infusion	Intravenous use	500 mg/10 ml for injection or variable concentration for infusion
Sweden	AstraZeneca AB 151 85 Södertälje Sweden	Meronem	1 g	Powder for solution for injection or infusion	Intravenous use	1g/20 ml for injection or variable concentration for infusion
United Kingdom	AstraZeneca UK Limited 600 Capability Green Luton Bedfordshire LU1 3LU United Kingdom	Meronem IV 500mg	500mg	Powder for solution for injection or infusion	Intravenous use	500 mg/20 ml
United Kingdom	AstraZeneca UK Limited 600 Capability Green Luton Bedfordshire LU1 3LU United Kingdom	Meronem IV 1g	1 g	Powder for solution for injection or infusion	Intravenous use	1g/30 ml

ANNEX II

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

SCIENTIFIC CONCLUSIONS

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

Meropenem is a member of the beta-lactam family of antibacterials and belongs to the class of carbapenems and is a broad-spectrum of *in vitro* antibacterial activity against Gram positive and Gram negative, aerobic and anaerobic pathogens, including extended-spectrum beta-lactamase (ESBL) and AMpC chromosomal beta-lactamase producing *Enterobacteriaceae*. It inhibits bacterial wall synthesis like other beta-lactam antibiotics, but is resistant to degradation by beta-lactamases or cephalosporinases.

The CHMP noted that the scope of this SPC harmonisation procedure covers two strengths (500 mg and 1g) of the unique IV pharmaceutical form.

A number of areas of disharmony in the product information for meropenem have been evaluated by the CHMP and the revised Product Information (PI) was adopted. The main areas for harmonisation were as follows.

- Quality issues

The MAH submitted a harmonisation of Module 3. The active substance meropenem trihydrate is manufactured by two manufacturers. Dainippon Sumitomo Pharma Co. Ltd. (Oita, Japan), was the originator and ACS Dobfar SpA (Milano / Italy) is an alternative manufacturer of both the intermediate HECA, and the pure sterile meropenem trihydrate. The latter manufacturer is also approved in the majority of the MSs and is therefore also mentioned in the harmonised documentation.

The information presented reflects that currently approved for Dainippon Sumitomo Pharma and for ACS Dobfar SpA, and includes additional information and the changes that have taken place up to date.

The information submitted in the Quality module concerning the stability of the products is completed with the most recent commercial data which support the shelf life of 4 years when the products are stored at up to 30 ºC.

Sections of the SPC pertaining to the quality aspects of the dossier, in particular sections 6.3 and 6.4 were also harmonised. The MAH has undertaken to submit further data within the specified time frame specified in their letter of undertaking dated 23 July 2009.

- Safety and Efficacy issues

Section 4.1 – Therapeutic Indications

Pneumonia, including community acquired pneumonia and nosocomial pneumonia

The clinical programme submitted at the time of the original MAA application described 6 clinical studies in approximately 1200 patients, of which approximately 650 were treated with meropenem. These studies recruited patients with LRTI, which was appropriate at that time. The MAH provided an overview of the pathogens relevant to LRTI, including MIC summary data for the common LRTI pathogens isolated.

Although it is acknowledged that not all patients with community-acquired pneumonia (CAP) require treatment with a carbapenem the MAH argued that restriction of the indication to severe cases only is

not required since severity is already implied by the route of administration of the product and other aspects of labelling. Taking all the information into consideration, the CHMP considered that there was no compulsory need to qualify the CAP as it is not expected that a health practitioner would resort to the use of an intravenous agent for treating mild CAP.

In contrast, taking into account the intended pathogens and the potential severity of these infections, the recent clinical studies, clinical practice, current microbiological context, international and national guidances, and considering the good use of antibiotics, meropenem can be considered as an appropriate antibacterial therapy in hospital acquired pneumonia (HAP). Although the bacteriology of nosocomial pneumonia and ventilator-associated pneumonia (VAP) are similar, the severity of the general condition of the patients and treatment outcome are sufficiently different to consider that efficacy in VAP cannot be extrapolated from efficacy in nosocomial pneumonia. Furthermore, meropenem has not been formally evaluated in a clinical trial for VAP. It was therefore accepted by the CHMP that the severity of the general condition of the patients and treatment outcome are sufficiently different to prevent the extrapolation of efficacy in VAP from the efficacy in HAP.

The CHMP finally agreed the following indication:

Pneumonia, including community acquired pneumonia and nosocomial pneumonia

It should also be noted that considerations for pneumonia are the same for adults and for children. Regarding the paediatric population, the CHMP is in agreement with the MAH to mention "3 months" as the lower limit of age but considers that the option of treating children under 3 months including neonates should be retained.

Broncho-pulmonary infections in cystic fibrosis (CF)

The clinical programme submitted at the time of the original MAA application described 1 clinical study in 40 patients, of which 27 were treated with meropenem. Data from this and a further study, of 122 patients (of whom 70 received meropenem in combination with tobramycin), conducted since the first registration show that meropenem is effective in the treatment of LRTI in patients with CF, and similar in effectiveness to ceftazidime alone or in combination with tobramycin. MIC summary data for the common lung pathogens in patients with CF isolated from two studies were also presented.

Recent susceptibility data for European isolates from various surveillance programmes and in light of clinical data, AstraZeneca propose that *P. aeruginosa* and *Burkholderia cepacia* will be listed under species that may be resistant to meropenem. Although other drugs do have activity against *P. aeruginosa*, specialists prefer to have a choice of agents to overcome issues of temporary reductions in susceptibility (i.e. antibiotic cycling), allergy or other intolerances. Most specialists would recommend using combinations of antibiotics to treat patients with CF, including combinations administered intravenously, orally, or by inhalation. The MAH discussed the evidence of benefit with Meronem derived from trials, national and international named patient/compassionate use data and comparative studies. Alternative therapies were also discussed. Improvement in lung function following an acute pulmonary exacerbation in CF is important to the quality of life and survival of the patient since lung function is the best predictor of mortality. Therefore, improvement in lung function is the key benefit to be derived from treatment with meropenem. Adequate clinical trial data to conduct a robust benefit assessment is sparse in CF, but two recent studies evaluating meropenem in combination with tobramycin were discussed by the MAH, one of which remains one of the largest trials undertaken in CF. An improvement in lung function is also evident from meropenem-treated CF patients from two compassionate use programs discussed by the MAH.

The safety of Meronem in CF derived from trials, national and international named patient/compassionate use data and comparative studies between meropenem and tobramycin or ceftazidim was also discussed. The MAH also searched the patient safety database for cases with a medical history of CF. A total of 484 events were identified in 273 cases, which were summarised and

discussed by the MAH. No reports of adverse events associated with inhaled or nebulised meropenem have been received by the MAH. Based on the discussed data, the MAH concluded that the safety profile reported in the population of patients with CF is similar to that reported overall and that meropenem is well tolerated. Nausea and changes in tests of liver function are among the commonest risks and these findings were reversible on discontinuation.

The CHMP considered the MAH arguments to be satisfactory, and agreed that the specific mention of cystic fibrosis in the indication section should be placed just under lower respiratory tract infections:

Broncho-pulmonary infections in cystic fibrosis

Regarding the paediatric population, the CHMP agreed with the MAH to mention "3 months" as the lower limit of age but considered that the option of treating children under 3 months including neonates should be retained.

Complicated urinary tract infections (cUTI)
To date, 7 AstraZeneca (AZ) sponsored studies have been conducted in UTIs. All of these studies (1 pivotal and 6 supportive) have been previously submitted in the original MAA. For the AZ studies, complicated UTI was associated with structural and/or functional abnormalities such as prostatic hypertrophy, hydronephrosis, neurogenic bladder, vesicoureteric reflux, stricture, calculus, tumour, upper UTI or prolapse, indwelling urinary catheter, or concomitant urologic diagnostic or surgical procedure. MIC summary data was also included.

The appropriateness of carbapenems including meropenem in UTI is supported by the clinical studies and the clinical experience. Clinical guidance recommends penems in cUTI without distinction of drugs regarding efficacy and safety. Consequently, taking into account the knowledge of the pharmacological class of -penems, the current microbiological context, the clinical practice and the clinical recommendations, the medical need of penems in some situations, and considering that meropenem should be used only in severe bacterial infections suspected or due to pathogens resistant to other beta-lactams and susceptible to meropenem, the CHMP considered that the following meropenem wording of the SPC therapeutic indication was acceptable:

Complicated urinary tract infections

It should be noted that considerations for cUTI are the same for adults and for children. Regarding the paediatric population, the CHMP agreed with the MAH to mention "3 months" as the lower limit of age but considered that the option of treating children under 3 months including neonates should be retained.

Complicated intra-abdominal infections

The clinical programme submitted at the time of the original MAA application described 5 clinical studies in approximately 1150 patients with IAI, of which approximately 580 were treated with meropenem. Since the original MAA application, 5 further clinical studies have been conducted in approximately 650 patients (data regarding numbers of patients treated with meropenem are not available). The MAH also listed the pathogens relevant to IAI, including MIC summary data for the common IAI pathogens isolated from the clinical studies.

The CHMP noted that the proposed indication in complicated IAIs is in accordance with the clinical documentation and the clinical experience gained in this field. Meropenem is mentioned as a recommended drug in therapeutic guidelines and the indication "Intra-abdominal infections" is approved in all 29 European countries. Consequently the CHMP agreed that the wording of the therapeutic indication was appropriate as follows:

Complicated intra-abdominal infections

The considerations for IAI are the same for adults and for children. Regarding the paediatric population, the CHMP agreed with the MAH to mention "3 months" as the lower limit of age but considered that the option of treating children under 3 months including neonates should be retained.

Intra- and post-partum infections

The clinical programme submitted at the time of the original MAA application described 1 clinical study in approximately 500 patients with obstetric and gynaecological infections, of which approximately 250 were treated with meropenem. Data from this study showed that meropenem was highly effective in the treatment of bacterial gynaecological infections. The clinical and bacteriological effectiveness of meropenem as monotherapy was similar to the combination treatment of clindamycin plus gentamicin. MIC summary data for the common gynaecological pathogens isolated from the clinical study presented in the original MAA are presented

The CHMP considered that it would be artificial to put emphasis on some sub-gynaecological infections as the level of demonstration was limited overall for gynaecological infections and especially when scrutinizing specific sub-indications such as episiotomy, endometritis. Therefore, the CHMP considered it more appropriate to group these sub-indications under general terms and therefore agreed the following indication:

Intra- and post-partum infections

It was noted that this indication was claimed for adults and children, but no paediatric posology recommendation were proposed by the MAH, however, this is accepted given the claimed gynaecological infections.

Complicated skin and skin structure infections (cSSSI)

The clinical programme submitted at the time of the original MAA application described 6 clinical studies in approximately 950 patients with SSSIs, of which approximately 470 were treated with meropenem. Since the original MAA application, 2 further clinical studies have been conducted in approximately 1050 patients, of which approximately 520 patients received meropenem.

The CHMP considered that the clinical documentation submitted by the MAH did not greatly contribute to the assessment as the studies include a mix of wide cutaneous infections without a robust documentation on severe cellulitis, not completely relevant considering the interest of penems. However, the interest to use carbapenems including meropenem in cSSSI is now supported by the clinical experience. Consequently, taking into account the microbiological activity of -penems, the current microbiological context, the clinical practice, the medical need of penems in some situations, and the fact that meropenem is intended only in severe bacterial infections suspected or due to pathogens resistant to other beta-lactams and susceptible to meropenem, the CHMP considered the following indication to be acceptable:

Complicated skin and skin tissue infections

It was noted that considerations for cSSSI are the same for adults and for children. Regarding the paediatric population, the CHMP agreed with the MAH to mention "3 months" as the lower limit of age but considered that the option of treating children under 3 months including neonates should be retained.

Acute bacterial meningitis

The clinical programme submitted at the time of the original MAA application describes 4 clinical studies in approximately 220 patients with meningitis infections, of which approximately 120 were

treated with meropenem. Data from these studies showed that meropenem was effective in the treatment of bacterial meningitis, and similar in effectiveness to cefotaxime/ceftriaxone. MIC summary data for the common meningitis pathogens isolated from the clinical studies presented in the original MAA.

Studies 3591IL/0065 and 3591IL/0022 included only paediatric patients but studies 3591IL/0020 and 3591IL/0021 included both paediatric and adult patients. The adequacy of meropenem to treat acute bacterial meningitis in adults is based upon the evaluation in adults referred to above, plus an extrapolation of efficacy from the much larger group of children with meningitis also evaluated. This extrapolation is considered valid because the pathophysiology of meningitis and its bacterial aetiology are essentially the same in adults and children, with knowledge of the dose relationship between adults and children (40 mg/kg in children is equivalent to a 2 g unit dose in adults).

Nevertheless, despite the inadequate clinical data provided the critical interest of this drug should not be disregarded, especially in resistant Gram negative strains producing extended spectrum beta-lactamase. The use of meropenem in meningitis is now considered as supported by the clinical experience and recognized in the therapeutic guidelines. Consequently taking into account the microbiological activity of meropenem, the current microbiological context, the clinical practice, the medical need of penems in some situations, and the fact that meropenem is intended only in severe bacterial infections suspected or due to pathogens resistant to other beta-lactams and susceptible to meropenem, the CHMP considered the indication “acute bacterial meningitis” to be acceptable.

Regarding the paediatric population, the CHMP agreed with the MAH to mention “3 months” as the lower limit of age but considered that the option of treating children under 3 months including neonates should be retained. The CHMP considered that although the level of demonstration was more limited in adults than in children, meropenem is an adequate option for also treating adult cases of acute meningitis.

The following wording was therefore agreed by the CHMP:

Acute bacterial meningitis

Treatment of febrile neutropenic patients

The clinical programme submitted at the time of the original MAA application described 2 clinical studies in approximately 470 patients, of which approximately 230 were treated with meropenem.

The CHMP noted that the indication of neutropenia is currently approved in most of the Member States. The interest to use meropenem as an empirical treatment for febrile neutropenia is supported by the clinical experience and is recognized in the therapeutic guidelines. Consequently taking into account the bacteria involved in this situation, the current microbiological context, the clinical practice, the medical need of penems in some cases, and the fact that meropenem is intended only in severe bacterial infections suspected or due to pathogens resistant to other beta-lactams and susceptible to meropenem, the CHMP considered that the indication for the *treatment of febrile neutropenia* could be accepted.

It was noted that considerations are the same for adults and children. Regarding the paediatric population, the CHMP agreed with the MAH to mention “3 months” as the lower limit of age but considered that the option of treating children under 3 months including neonates should be retained.

The CHMP agreed the following harmonised indication:

Meronem may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection

From a conceptual perspective, combinations of antibacterials from different classes may cover unsuspected pathogens, improve coverage for antibiotic-resistant pathogens like *P. aeruginosa*, prevent or reduce antibiotic resistance and achieve better clinical and bacteriological outcomes. This may also help to reduce resistance through reducing horizontal transmission of inadequately treated infections due to antibiotic-resistant pathogens. The decision to use meropenem as part of a combination regimen will be made by health care professionals taking into account individual patient characteristics, the infection being treated, the predominant local bacterial flora and their antibiotic susceptibility profiles.

The safety profile is based primarily on monotherapy clinical trials and the numbers of post marketing reports of adverse events of patients receiving bi-therapy are small, therefore it would not be possible to extrapolate from these.

The CHMP considered that there was no compulsory need for a specific statement on combination strategies in the SPC since the clinical practice is guided by official guidance, as referred to in section 4.1 of the SPC:

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

Section 4.2 - Posology and method of administration

In summary, the CHMP harmonised the posology, for both adults and adolescents, and children over 50 kg body weight of 500 mg or 1 g (to be administered every 8 hours) and for children from 3 months (and under) to 11 years of age and up to 50 kg body weight a dose of 10 or 20 mg/kg (administered every 8 hours) for the following indications:

- Pneumonia , including community acquired pneumonia and nosocomial pneumonia
- Complicated urinary tract infections
- Complicated intra-abdominal infections
- Intra- and post-partum infections (for adults only)
- Complicated skin and skin tissue infections

For the indications above, the CHMP, considering the safety profile of the drug, was of the view that dosing beyond 1g in IV bolus in adults and 20 mg/kg IV bolus in children should not be exceeded. The CHMP agreed to add the following statement in section 4.2 of the SPC:

Limited safety data are available to support the 2 g intravenous bolus or the corresponding paediatric 40 mg/kg bolus

For broncho-pulmonary infections in cystic fibrosis **t**he CHMP agreed with the MAH proposal for the dosage regimen including the posology 2g/8h in adults and adolescents and children over 50 kg body weight, and 40 mg/kg q8h in children from 3 months (and under) to 11 years of age and up to 50 kg body weight, as higher doses are specifically requested in the treatment of infections due to *Acinetobacter* or *P. aeruginosa.* Lower doses to treat such infections have to be avoided because of the risk of sub-optimal concentrations.

For the indication acute bacterial meningitis the CHMP agreed with the MAH proposal concerning the dosage regimen including exclusively higher doses of 2 g to be administered every 8 hours for both adults and adolescents, and children over 50 kg body weight. For children from 3 months (and under) to 11 years of age and up to 50 kg body weight a dose of 40 mg/kg administered every 8 hours was agreed.

For all indications no dose adjustment was considered to be necessary in hepatically impaired patients and in the elderly with normal renal function or creatinine clearance values above 50ml/min, for all indications. Regarding the posology in elderly, the CHMP considered that being above 65 years of age does not *per se* constitute a problem for the drug administration, unless the clinical status and renal function of the patient are significantly altered.

Regarding the dosage schedule for adults with impaired renal function, the MAH stated that dose adjustments of the upper limit from 1 g to 2 g had not been studied but are widely used in clinical practice.

The MAH's recommendation for administration over 15 to 30 minutes is based on dosage recommendations used in the efficacy studies conducted to support the registration of meropenem.

Section 4.3 - Contra-indications

The CHMP agreed with the following information added by the MAH in section 4.3 of the SPC on hypersensitivity to any other carbapenem antibacterial agent and severe hypersensitivity (eg anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (eg penicillins or cephalosporins).

Hypersensitivity to any other carbapenem antibacterial agent.
Severe hypersensitivity (eg anaphylactic reaction, severe skin reaction) to any other type of betalactam antibacterial agent (e.g. penicillins or cephalosporins).

Section 4.4 - Special warnings and precautions for use

The CHMP noted that the safety profile of meropenem is well-known and that hypersensitivity including serious reactions is considered typical for the carbapenem class. Considering this, Section 4.4 was revised with amendments to the paragraphs on hypersensitivity and the gastro-intestinal system.

The CHMP proposed to retain the information on convulsions and hepatic reactions as such statement warrants the attention of prescribers on the need for careful use of meropenem, taking into account both adverse events.

The CHMP considered that the information submitted by the MAH was insufficient and not convincing enough to allow the deletion of the monitoring of the treatment due to hepatic toxicity.

Section 4.5 - Interaction with other medicinal products and other forms of interaction

The CHMP considered that co-administration of probenecid and meropenem is not expected to have clinical consequences, in view of the limited increase. The CHMP agreed that valproic acid should be avoided during treatment with Meronem. Finally, with regards to the potential interaction with anticoagulants, the CHMP maintains its position that oral anticoagulants effects may be augmented when used concomitantly with antibiotics

Section 4.6 - Pregnancy and lactation

The CHMP agreed with the updated harmonised wording proposed for the sections Pregnancy and Lactation in section 4.6, that was in line with the 'Guideline on risk assessment of medicinal products on human reproduction and lactation (EMEA/CHMP/203927/2005, July 2008)'

Section 4.7 - Effects on ability to drive and use machines

No data is available, but it is not expected that Meronem will affect the ability to drive or use machines.
The CHMP agreed with the statement proposed by the MAH.

Section 4.8 - Undesirable effects

The CHMP noted that the data from studies or reviews provided by the MAH reported a few cases of convulsions with meropenem. Therefore, as this reaction is considered relevant for the carbapenem class and as a wording has been mentioned in Section 4.4 of the SPC of other carbapenems, the CHMP agreed on the following statement in Section 4.4 of the Meronem SPC:

Seizures have infrequently been reported during treatment with carbapenems, including meropenem (see section 4.8).

Therefore, the CHMP agreed that the two ADRs "blood creatinine increased" and "blood urea increased" should be included in the harmonised SPC for Meronem as 'uncommon ADRs'.

Section 4.9 – Overdose

The CHMP agreed that intentional overdosing of Meronem is unlikely, although unintentional overdosing could occur, particularly in patients with renal impairment. In individuals with normal renal function, rapid renal elimination will occur. Haemodialysis will remove Meronem and its metabolite.

Section 5.1 - Pharmacodynamic properties

The CHMP noted that EU countries themselves do not consider that CLSI breakpoints are required in addition to the EUCAST breakpoints. The CHMP therefore unanimously considered that there is no place for CLSI as soon as EUCAST breakpoints are available. Consequently the CLSI paragraph was deleted and only EUCAST information was specified for this harmonised EU SPC.
Revisions were also made to the table of antibacterial spectrum.

Finally, the "Species for which acquired resistance may be a problem" and the "Inherently resistant organisms" were revised.

Section 5.2 - Pharmacokinetic properties

The CHMP noted the MAH proposal for this section, and considered it acceptable. In particular the sub-section specific for neonates was appreciated. The CHMP adopted a harmonised text for this section.

Section 5.3 - Preclinical safety data

The CHMP considered that meropenem has a relatively low acute toxicity, even though effects on the kidney were seen in mice at 2200 mg/kg, dogs at 2000 mg/kg and monkeys at 500mg/kg. The CHMP agreed to the additional modifications in this section of the SPC, mentioning the effects on the kidney in mice, dogs and monkeys.
Additional modifications mentioning the effects on the CNS in rodents were also added to section 5.3 of the SPC.

Section 6.1 - List of excipients

Based on the Quality data submitted, the CHMP agreed that anhydrous sodium carbonate is the only inactive ingredient in the product. It was added to aid in the dissolution of the bulk drug by increasing the pH of the solution above the pKa value of the carboxyl group of meropenem.

Section 6.2 - Incompatibilities

Based on the Quality data submitted, the CHMP agreed that this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Section 6.3 - Shelf life

The data submitted in the Quality module concerning the stability of the products is completed with the most recent commercial data which support the shelf life of 4 years when the products are stored at up to 30 ºC. The CHMP agreed that there should be an "immediate use" of reconstituted solutions, especially since very rapid degradation of Glucose 5% occurs. Therefore, section 6.3 of the SPC states that reconstituted solutions are to be used within 1 hour (this covers the preparation of the reconstituted solution and the duration of intravenous injection or infusion of the reconstituted solution).

Section 6.4 - Special precautions for storage

Based on the Quality data submitted, the CHMP concluded that the product should not be stored above 30°C and that the reconstituted solution should not be frozen.

Section 6.5 - Nature and contents of container

Based on the Quality data submitted, the CHMP revised the text in this section and stated that the medicinal product is supplied in pack sizes of 1 or 10 vials and that not all pack sizes may be marketed.

Section 6.6 - Special precautions for disposal and other handling

Based on the Quality data submitted, the CHMP concluded that meropenem to be used for bolus intravenous injection should be constituted with sterile water for injection and that for intravenous infusion, meropenem vials may be directly constituted with 0.9 % sodium chloride or 5 % glucose solutions for infusion.

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

Whereas

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

- the Summary 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 has recommended the amendment of the Marketing Authorisation(s) for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Meronem and associated names (see Annex I). The conditions of the Marketing Authorisation are listed in Annex IV.

ANNEX III

**SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET**

Note: This SPC, labelling and packages leaflet is the version valid at the time of Commission Decision.

After the Commission Decision the Member State Competent Authorities, in liaison with the Reference Member State, will update the product information as required. Therefore, this SPC, labelling and package leaflet may not necessarily represent the current text.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Meronem and associated names (see Annex I) 500 mg powder for solution for injection or infusion
Meronem and associated names (see Annex I) 1 g powder for solution for injection or infusion

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Meronem and associated names (see Annex I) 500 mg

Each vial contains meropenem trihydrate equivalent to 500 mg anhydrous meropenem.

Meronem and associated names (see Annex I) 1 g
Each vial contains meropenem trihydrate equivalent to 1 g anhydrous meropenem.

Excipients:
Each 500 mg vial contains 104 mg sodium carbonate which equates to approximately 2.0 mEq of sodium (approximately 45 mg).
Each 1 g vial contains 208 mg sodium carbonate which equates to approximately 4.0 mEq of sodium (approximately 90 mg).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

A white to light yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Meronem is indicated for the treatment of the following infections in adults and children over 3 months of age (see sections 4.4 and 5.1):

- Pneumonia, including community acquired pneumonia and nosocomial pneumonia.
- Broncho-pulmonary infections in cystic fibrosis
- Complicated urinary tract infections
- Complicated intra-abdominal infections
- Intra- and post-partum infections
- Complicated skin and soft tissue infections
- Acute bacterial meningitis

Meronem may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

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

4.2 Posology and method of administration

The tables below provide general recommendations for dosing.

The dose of meropenem administered and the duration of treatment should take into account the type of infection to be treated, including its severity, and the clinical response.

A dose of up to 2 g three times daily in adults and adolescents and a dose of up to 40 mg/kg three times daily in children may be particularly appropriate when treating some types of infections, such as nosocomial infections due to *Pseudomonas aeruginosa* or *Acinetobacter* spp.

Additional considerations for dosing are needed when treating patients with renal insufficiency (see further below).

Adults and adolescents

Infection	Dose to be administered every 8 hours
Pneumonia including community-acquired pneumonia and nosocomial pneumonia.	500 mg or 1 g
Broncho-pulmonary infections in cystic fibrosis	2 g
Complicated urinary tract infections	500 mg or 1 g
Complicated intra-abdominal infections	500 mg or 1 g
Intra- and post-partum infections	500 mg or 1 g
Complicated skin and soft tissue infections	500 mg or 1 g
Acute bacterial meningitis	2 g
Management of febrile neutropenic patients	1 g

Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes (see section 6.2, 6.3 and 6.6).

Alternatively, doses up to 1 g can be given as an intravenous bolus injection over approximately 5 minutes. There are limited safety data available to support the administration of a 2 g dose in adults as an intravenous bolus injection.

Renal impairment
The dose for adults and adolescents should be adjusted when creatinine clearance is less than 51 ml/min, as shown below. There are limited data to support the application of these dose adjustments for a unit dose of 2 g.

Creatinine clearance (ml/min)	Dose (based on "unit" dose range of 500 mg or 1 g or 2 g, see table above)	Frequency
26-50	one unit dose	every 12 hours
10-25	half of one unit dose	every 12 hours
<10	half of one unit dose	every 24 hours

Meropenem is cleared by haemodialysis and haemofiltration. The required dose should be administered after completion of the haemodialysis cycle.

There are no established dose recommendations for patients receiving peritoneal dialysis.

Hepatic impairment
No dose adjustment is necessary in patients with hepatic impairment (see section 4.4).

Dose in elderly patients
No dose adjustment is required for the elderly with normal renal function or creatinine clearance values above 50 ml/min.

Paediatric population

Children under 3 months of age
The safety and efficacy of meropenem in children under 3 months of age have not been established and the optimal dose regimen has not been identified. However, limited pharmacokinetic data suggest that 20 mg/kg every 8 hours may be an appropriate regimen (see section 5.2).

Children from 3 months to 11 years of age and up to 50 kg body weight
The recommended dose regimens are shown in the table below:

Infection	Dose to be administered every 8 hours
Pneumonia including community-acquired pneumonia and nosocomial pneumonia	10 or 20 mg/kg
Broncho-pulmonary infections in cystic fibrosis	40 mg/kg
Complicated urinary tract infections	10 or 20 mg/kg
Complicated intra-abdominal infections	10 or 20 mg/kg
Complicated skin and soft tissue infections	10 or 20 mg/kg
Acute bacterial meningitis	40 mg/kg
Management of febrile neutropenic patients	20 mg/kg

Children over 50 kg body weight,
The adult dose should be administered.

There is no experience in children with renal impairment.

Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes (see sections 6.2, 6.3, and 6.6). Alternatively, meropenem doses of up to 20 mg/kg may be given as an intravenous bolus over approximately 5 minutes. There are limited safety data available to support the administration of a 40 mg/kg dose in children as an intravenous bolus injection.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Hypersensitivity to any other carbapenem antibacterial agent.
Severe hypersensitivity (eg anaphylactic reaction, severe skin reaction) to any other type of betalactam antibacterial agent (e.g. penicillins or cephalosporins)

4.4 Special warnings and precautions for use

The selection of meropenem to treat an individual patient should take into account the appropriateness of using a carbapenem antibacterial agent based on factors such as severity of the infection, the prevalence of resistance to other suitable antibacterial agents and the risk of selecting for carbapenem-resistant bacteria.

As with all beta-lactam antibiotics, serious and occasionally fatal hypersensitivity reactions have been reported (see sections 4.3 and 4.8).

Patients who have a history of hypersensitivity to carbapenems, penicillins or other beta-lactam antibiotics may also be hypersensitive to meropenem. Before initiating therapy with meropenem, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics.

If a severe allergic reaction occurs, the medicinal product should be discontinued and appropriate measures taken.

Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all anti-bacterial agents, including meropenem, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of meropenem (see section 4.8). Discontinuation of therapy with meropenem and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Seizures have infrequently been reported during treatment with carbapenems, including meropenem (see section 4.8).

Hepatic function should be closely monitored during treatment with meropenem due to the risk of hepatic toxicity (hepatic dysfunction with cholestasis and cytolysis) (see section 4.8).

Use in patients with liver disease: patients with pre-existing liver disorders should have liver function monitored during treatment with meropenem. There is no dose adjustment necessary (see section 4.2).

A positive direct or indirect Coombs test may develop during treatment with meropenem.

The concomitant use of meropenem and valproic acid/sodium valproate is not recommended (see section 4.5).

Meronem contains sodium.

Meronem 500 mg: This medicinal product contains approximately 2.0 mEq of sodium per 500 mg dose which should be taken into consideration by patients on a controlled sodium diet.

Meronem 1.0 g: This medicinal product contains approximately 4.0 mEq of sodium per 1.0 g dose which should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No specific medicinal product interaction studies other than probenecid were conducted.
Probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem with the effect of increasing the elimination half-life and plasma concentration of meropenem. Caution is required if probenecid is co-administered with meropenem.

The potential effect of meropenem on the protein binding of other medicinal products or metabolism has not been studied. However, the protein binding is so low that no interactions with other compounds would be expected on the basis of this mechanism.

Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60-100 % decrease in valproic acid levels in about two days. Due to the rapid onset and the extent of the decrease, co-administration of valproic acid with carbapenem agents is not considered to be manageable and therefore should be avoided (see section 4.4).

Oral anti-coagulants
Simultaneous administration of antibiotics with warfarin may augment its anti-coagulant effects. There have been many reports of increases in the anti-coagulant effects of orally administered anti-

coagulant agents, including warfarin in patients who are concomitantly receiving antibacterial agents. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the antibiotic 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 antibiotics with an oral anti-coagulant agent.

4.6 Pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of meropenem in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of meropenem during pregnancy.

Lactation
It is unknown whether meropenem is excreted in human milk. Meropenem is detectable at very low concentrations in animal breast milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from meropenem therapy taking into account the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed.

4.8 Undesirable effects

In a review of 4,872 patients with 5,026 meropenem treatment exposures, meropenem-related adverse reactions most frequently reported were diarrhoea (2.3 %), rash (1.4 %), nausea/vomiting (1.4 %) and injection site inflammation (1.1 %). The most commonly reported meropenem-related laboratory adverse events were thrombocytosis (1.6 %) and increased hepatic enzymes (1.5-4.3 %).

Adverse reactions listed in the table with a frequency of "not known" were not observed in the 2,367 patients who were included in pre-authorisation clinical studies with intravenous and intramuscular meropenem but have been reported during the post-marketing period.

In the table below all adverse reactions are listed by system organ class and frequency: very common (≥ 1/10); 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) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1

System Organ Class	Frequency	Event
Infections and infestations	Uncommon	oral and vaginal candidiasis
Blood and lymphatic system disorders	Common	thrombocythaemia
	Uncommon	eosinophilia, thrombocytopenia, leucopenia, neutropenia
	Not known	agranulocytosis, haemolytic anaemia
Immune system disorders	Not known	angioedema, anaphylaxis (see sections 4.3 and 4.4)
Nervous system disorders	Common	headache
	Uncommon	paraesthesiae
	Rare	convulsions (see section 4.4)
Gastrointestinal disorders	Common	diarrhoea, vomiting, nausea,

System Organ Class	Frequency	Event
		abdominal pain
	Not known	antibiotic-associated colitis (see section 4.4)
Hepatobiliary disorders	Common	transaminases increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased.
	Uncommon	blood bilirubin increased
Skin and subcutaneous tissue disorders	Common	rash, pruritis
	Uncommon	urticaria
	Not known	toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme.
Renal and urinary disorders	Uncommon	blood creatinine increased, blood urea increased
General disorders and administration site conditions	Common	inflammation, pain
	Uncommon	thrombophlebitis
	Not known	pain at the injection site

4.9 Overdose

Relative overdose may be possible in patients with renal impairment if the dose is not adjusted as described in section 4.2. Limited post-marketing experience indicates that if adverse reactions occur following overdose, they are consistent with the adverse reaction profile described in section 4.8, are generally mild in severity and resolve on withdrawal or dose reduction. Symptomatic treatments should be considered.

In individuals with normal renal function, rapid renal elimination will occur.

Haemodialysis will remove meropenem and its metabolite.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, carbapenems, ATC code: J01DH02

Mode of action

Meropenem exerts its bactericidal activity by inhibiting bacterial cell wall synthesis in Gram-positive and Gram-negative bacteria through binding to penicillin-binding proteins (PBPs).

Pharmacokinetic/Pharmacodynamic (PK/PD) relationship

Similar to other beta-lactam antibacterial agents, the time that meropenem concentrations exceed the MIC (T>MIC) has been shown to best correlate with efficacy. In preclinical models meropenem demonstrated activity when plasma concentrations exceeded the MIC of the infecting organisms for approximately 40 % of the dosing interval. This target has not been established clinically.

Mechanism of resistance

Bacterial resistance to meropenem may result from: (1) decreased permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins) (2) reduced affinity of the target PBPs (3) increased expression of efflux pump components, and (4) production of beta-lactamases that can hydrolyse carbapenems.

Localised clusters of infections due to carbapenem-resistant bacteria have been reported in the European Union.

There is no target-based cross-resistance between meropenem and agents of the quinolone, aminoglycoside, macrolide and tetracycline classes. However, bacteria may exhibit resistance to more than one class of antibacterials agents when the mechanism involved include impermeability and/or an efflux pump(s).

Breakpoints

European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints for MIC testing are presented below.

EUCAST clinical MIC breakpoints for meropenem (2009-06-05, v 3.1)

Organism	Susceptible (S) (mg/l)	Resistant (R) (mg/l)
Enterobacteriaceae	≤ 2	> 8
Pseudomonas	≤ 2	> 8
Acinetobacter	≤ 2	> 8
Streptococcus groups A, B, C, G	≤ 2	> 2
Streptococcus pneumoniae[1]	≤ 2	> 2
Other streptococci	2	2
Enterococcus	--	--
Staphylococcus[2]	note 3	note 3
Haemophilus influenzae[1] and *Moraxella catarrhalis*	≤ 2	> 2
Neisseria meningitidis[2,4]	≤ 0.25	> 0.25
Gram-positive anaerobes	≤ 2	> 8
Gram-negative anaerobes	≤ 2	> 8
Non-species related breakpoints[5]	≤ 2	> 8

[1] Meropenem breakpoints for *Streptococcus pneumoniae* and *Haemophilus influenzae* in meningitis are 0.25/1 mg/L.

[2] Strains with MIC values above the S/I breakpoint are rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported as resistant.

[3] Susceptibility of staphylococci to meropenem is inferred from the methicillin susceptibility.

[4] Meropenem breakpoints in *Neisseria meningitidis* relates to meningitis only.

[5] Non-species related breakpoints have been determined mainly from PK/PD data and are independent of the MIC distributions of specific species. They are for use for species not mentioned in the table and footnotes.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the medicinal product.

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.

The following table of pathogens listed is derived from clinical experience and therapeutic guidelines.

Commonly susceptible species
Gram-positive aerobes
Enterococcus faecalis[$]
Staphylococcus aureus (methicillin-susceptible)[£]
Staphylococcus species (methicillin-susceptible) including *Staphylococcus epidermidis*
Streptococcus agalactiae (Group B)
Streptococcus milleri group *(S. anginosus, S. constellatus, and S. intermedius)*
Streptococcus pneumoniae
Streptococcus pyogenes (Group A)

Gram-negative aerobes
Citrobacter freudii
Citrobacter koseri
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Morganella morganii
Neisseria meningitidis
Proteus mirabilis
Proteus vulgaris
Serratia marcescens

Gram-positive anaerobes
Clostridium perfringens
Peptoniphilus asaccharolyticus
Peptostreptococcus species *(including P. micros, P anaerobius, P. magnus)*

Gram-negative anaerobes
Bacteroides caccae
Bacteroides fragilis group
Prevotella bivia
Prevotella disiens

Species for which acquired resistance may be a problem
Gram-positive aerobes
Enterococcus faecium[$†]

Gram-negative aerobes
Acinetobacter species
Burkholderia cepacia
Pseudomonas aeruginosa

Inherently resistant organisms
Gram-negative aerobes
Stenotrophomonas maltophilia
Legionella species

Other micro-organisms
Chlamydophila pneumoniae
Chlamydophila psittaci
Coxiella burnetii
Mycoplasma pneumoniae

[$]Species that show natural intermediate susceptibility
[£]All methicillin-resistant staphylococci are resistant to meropenem
[†]Resistance rate ≥ 50% in one or more EU countries.

5.2 Pharmacokinetic properties

In healthy subjects the mean plasma half-life is approximately 1 hour; the mean volume of distribution is approximately 0.25 l/kg (11-27 l) and the mean clearance is 287 ml/min at 250 mg falling to 205 ml/min at 2 g. Doses of 500, 1000 and 2000 mg doses infused over 30 minutes give mean Cmax values of approximately 23, 49 and 115 µg/ml respectively, corresponding AUC values were 39.3, 62.3 and 153 µg.h/ml. After infusion over 5 minutes Cmax values are 52 and 112 µg/ml after 500 and 1000 mg doses respectively. When multiple doses are administered 8-hourly to subjects with normal renal function, accumulation of meropenem does not occur.

A study of 12 patients administered meropenem 1000 mg 8 hourly post-surgically for intra-abdominal infections showed a comparable Cmax and half-life to normal subjects but a greater volume of distribution 27 l.

Distribution

The average plasma protein binding of meropenem was approximately 2 % and was independent of concentration. After rapid administration (5 minutes or less) the pharmacokinetics are biexponential but this is much less evident after 30 minutes infusion. Meropenem has been shown to penetrate well into several body fluids and tissues: including lung, bronchial secretions, bile, cerebrospinal fluid, gynaecological tissues, skin, fascia, muscle, and peritoneal exudates.

Metabolism

Meropenem is metabolised by hydrolysis of the beta-lactam ring generating a microbiologically inactive metabolite. In vitro meropenem shows reduced susceptibility to hydrolysis by human dehydropeptidase-I (DHP-I) compared to imipenem and there is no requirement to co-administer a DHP-I inhibitor.

Elimination

Meropenem is primarily excreted unchanged by the kidneys; approximately 70 % (50 –75 %) of the dose is excreted unchanged within 12 hours. A further 28% is recovered as the microbiologically inactive metabolite. Faecal elimination represents only approximately 2% of the dose. The measured renal clearance and the effect of probenecid show that meropenem undergoes both filtration and tubular secretion.

Renal insufficiency

Renal impairment results in higher plasma AUC and longer half-life for meropenem. There were AUC increases of 2.4 fold in patients with moderate impairment (CrCL 33-74 ml/min), 5 fold in severe impairment (CrCL 4-23 ml/min) and 10 fold in haemodialysis patients (CrCL <2 ml/min) when compared to healthy subjects (CrCL >80 ml/min). The AUC of the microbiologically inactive ring opened metabolite was also considerably increased in patients with renal impairment. Dose adjustment is recommended for patients with moderate and severe renal impairment (see section 4.2).

Meropenem is cleared by haemodialysis with clearance during haemodialysis being approximately 4 times higher that in anuric patients.

Hepatic insufficiency

A study in patients with alcoholic cirrhosis shows no effect of liver disease on the pharmacokinetics of meropenem after repeated doses.

Adult patients

Pharmacokinetic studies performed in patients have not shown significant pharmacokinetic differences versus healthy subjects with equivalent renal function. A population model developed from data in 79 patients with intra-abdominal infection or pneumonia, showed a dependence of the central volume on weight and the clearance on creatinine clearance and age.

Paediatrics
The pharmacokinetics in infants and children with infection at doses of 10, 20 and 40 mg/kg showed Cmax values approximating to those in adults following 500, 1000 and 2000 mg doses, respectively. Comparison showed consistent pharmacokinetics between the doses and half-lives similar to those observed in adults in all but the youngest subjects (<6 months t1/2 1.6 hours). The mean meropenem clearance values were 5.8 ml/min/kg (6-12 years), 6.2 ml/min/kg (2-5 years), 5.3 ml/min/kg (6-23 months) and 4.3 ml/min/kg (2-5 months). Approximately 60 % of the dose is excreted in urine over 12 hours as meropenem with a further 12 % as metabolite. Meropenem concentrations in the CSF of children with meningitis are approximately 20 % of concurrent plasma levels although there is significant inter-individual variability.

The pharmacokinetics of meropenem in neonates requiring anti-infective treatment showed greater clearance in neonates with higher chronological or gestational age with an overall average half-life of 2.9 hours. Monte Carlo simulation based on a population PK model showed that a dose regimen of 20 mg/kg 8 hourly achieved 60 %T>MIC for *P. aeruginosa* in 95 % of pre-term and 91 % of full term neonates.

Elderly
Pharmacokinetic studies in healthy elderly subjects (65-80 years) have shown a reduction in plasma clearance, which correlated with age-associated reduction in creatinine clearance, and a smaller reduction in non-renal clearance. No dose adjustment is required in elderly patients, except in cases of moderate to severe renal impairment (see section 4.2).

5.3 Preclinical safety data

Animal studies indicate that meropenem is well tolerated by the kidney. Histological evidence of renal tubular damage was seen in mice and dogs only at doses of 2000 mg/kg and above after a single administration and above and in monkeys at 500 mg/kg in a 7-day study.

Meropenem is generally well tolerated by the central nervous system. Effects were seen in acute toxicity studies in rodent at doses exceeding 1000 mg/kg.

The IV LD_{50} of meropenem in rodents is greater that 2000 mg/kg.

In repeat dose studies of up to 6 months duration only minor effects were seen including a decrease in red cell parameters in dogs.

There was no evidence of mutagenic potential in a conventional test battery and no evidence of reproductive toxicity including teratogenic potential in studies in rats up to 750 mg/kg and in monkeys up to 360 mg/kg.

There was increased evidence of abortions at 500 mg/kg in a preliminary study in monkeys.

There was no evidence of increased sensitivity to meropenem in juveniles compared to adult animals. The intravenous formulation was well tolerated in animal studies.

The sole metabolite of meropenem had a similar profile of toxicity in animal studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Meronem 500 mg: anhydrous sodium carbonate
Meronem 1 g: anhydrous sodium carbonate

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

4 years

After reconstitution:
The reconstituted solutions for intravenous injection or infusion should be used immediately. The time interval between the beginning of reconstitution and the end of intravenous injection or infusion should not exceed one hour.

6.4 Special precautions for storage

Do not store above 30°C.
Do not freeze the reconstituted solution.

6.5 Nature and contents of container

Meronem 500 mg
674 mg powder in a 20 ml Type 1 glass vial with stopper (grey halobutilic rubber with an aluminium cap
Meronem 1 g
1348 mg powder in a 30 ml Type 1 glass vial with stopper (grey halobutilic rubber with an aluminium cap)

The medicinal product is supplied in pack sizes of 1 or 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Injection
Meropenem to be used for bolus intravenous injection should be constituted with sterile water for injection.

Infusion
For intravenous infusion meropenem vials may be directly constituted with 0.9 % sodium chloride or 5% glucose solutions for infusion.

Each vial is for single use only.

Standard aseptic techniques should be used for solution preparation and administration.

The solution should be shaken before use.

Any unused product or waste material should be disposed of in accordance with local 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

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Meronem and associated names (see Annex I) 500 mg powder for solution for injection or infusion
Meronem and associated names (see Annex I) 1 g powder for solution for injection or infusion

[See Annex I - To be completed nationally]

meropenem

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains meropenem trihydrate equivalent to 500 mg anhydrous meropenem.
Each vial contains meropenem trihydrate equivalent to 1 g anhydrous meropenem.

3. LIST OF EXCIPIENTS

Anhydrous sodium carbonate. See leaflet for information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection or infusion.
1 vial
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.
For single use only.

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

Do not store above 30°C
After reconstitution: The reconstituted solutions for intravenous injection or infusion should be used immediately. The time interval between the beginning of reconstitution and the end of intravenous injection or infusion should not exceed one hour.

Do not freeze the reconstituted solution

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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL (VIAL)

1. NAME OF THE MEDICINAL PRODUCT

Meronem and associated names (see Annex I) 500 mg powder for solution for injection or infusion
Meronem and associated names (see Annex I) 1 g powder for solution for injection or infusion

[See Annex I - To be completed nationally]

meropenem

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Meropenem trihydrate equivalent to 500 mg anhydrous meropenem
Meropenem trihydrate equivalent to 1 g anhydrous meropenem

3. LIST OF EXCIPIENTS

Anhydrous sodium carbonate. See leaflet for information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection or infusion.

1 vial
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C
After reconstitution: Use within one hour. Do not freeze.

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 }
<{ }>
<{ }>
<{ }>

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Meronem and associated names (see Annex I) 500 mg powder for solution for injection or infusion
Meronem and associated names (see Annex I) 1 g powder for solution for injection or infusion

[See Annex I - To be completed nationally]

meropenem

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 nurse.
- 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 nurse.

In this leaflet:

1. WHAT MERONEM IS AND WHAT IT IS USED FOR

Meronem belongs to a group of medicines called carbapenem antibiotics. It works by killing bacteria, which can cause serious infections.

- Infection affecting the lungs (pneumonia)
- Lung and bronchial infections in patients suffering from cystic fibrosis
- Complicated urinary tract infections
- Complicated infections in the abdomen
- Infections that you can catch during or after the delivery
- Complicated skin and soft tissues infections
- Acute bacterial infection of the brain (meningitis)

Meronem may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

2. BEFORE YOU USE MERONEM

Do not use Meronem
- if you are allergic (hypersensitive) to meropenem or any of the other ingredients of Meronem (listed in Section 6 Futher information).
- If you are allergic (hypersensitive) to other antibiotics such as penicillins, cephalosporins, or carbapenems as you may also be allergic to meropenem

Take special care with Meronem
Check with your doctor before using Meronem:

- if you have health problems, such as liver or kidney problems.
- if you have had severe diarrhoea after taking other antibiotics.

You may develop a positive test (Coombs test) which indicates the presence of antibodies that may destroy red blood cells. Your doctor will discuss this with you.

If you are not sure if any of the above applies to you, talk to your doctor or nurse before using Meronem.

Using other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription and herbal medicines.
This is because Meronem can affect the way some medicines work and some medicines can have an effect on Meronem.

In particular, tell your doctor or nurse if you are taking any of the following medicines:
- Probenecid (used to treat gout).
- Sodium valproate (used to treat epilepsy). Meronem should not be used because it may decrease the effect of sodium valproate.

Pregnancy and breast-feeding
It is important that you tell your doctor if you are pregnant or are planning to become pregnant before receiving meropenem. It is preferable to avoid the use of meropenem during pregnancy.
Your doctor will decide whether you should use Meropenem.

It is important that you tell your doctor if you are breast-feeding or if you intend to breast-feed before receiving meropenem. Small amounts of this medicine may pass into the breast milk and it may affect the baby. Therefore, your doctor will decide whether you should use Meropenem while breast-feeding.

Ask your doctor for advice before taking any medicine.

Driving and using machines
No studies on the effect on the ability to drive and use machines have been performed.

Important information about some of the ingredients of Meronem
Meronem contains sodium.

Meronem 500 mg: This medicinal product contains approximately 2.0 mEq of sodium per 500 mg dose which should be taken into consideration by patients on a controlled sodium diet.

Meronem 1.0 g: This medicinal product contains approximately 4.0 mEq of sodium per 1.0 g dose which should be taken into consideration by patients on a controlled sodium diet.

If you have a condition which requires you to monitor your sodium intake please inform your doctor or nurse.

3. HOW TO USE MERONEM

Adults
- The dose depends on the type of infection that you have, where the infection is in the body and how serious the infection is. Your doctor will decide on the dose that you need.
- The dose for adults is usually between 500 mg (milligrams) and 2 g (gram). You will usually receive a dose every 8 hours. However you may receive a dose less often if your kidneys do not work very well.

Children and adolescents

- The dose for children over 3 months old and up to 12 years of age is decided using the age and weight of the child. The usual dose is between 10 mg and 40 mg of Meronem for each kilogram (kg) that the child weighs. A dose is usually given every 8 hours. Children who weigh over 50 kg will be given an adult dose.
- Meronem will be given to you as an injection or infusion into a large vein.
- Your doctor or nurse will normally give Meronem to you.
- However, some patients, parents and carers are trained to give Meronem at home. Instructions for doing this are provided in this leaflet (in the section called 'Instructions for giving Meronem to yourself or someone else at home'). Always use Meronem exactly as your doctor has told you. You should check with your doctor if you are not sure.
- Your injection should not be mixed with or added to solutions that contain other medicines.
- The injection may take about 5 minutes or between 15 and 30 minutes. Your doctor will tell you how to give Meronem.
- You should normally have your injections at the same times each day.

If you use more Meronem than you should

If you accidentally use more than your prescribed dose, contact your doctor or nearest hospital straight away.

If you forget to use Meronem

If you miss an injection, you should have it as soon as possible. However, if it is almost time for your next injection, skip the missed injection.
Do not take a double dose (two injections at the same time) to make up for a forgotten dose.

If you stop using Meropenem

Do not stop having Meronem until your doctor tells you to.
If you have any further questions on the use of this product, ask your doctor or nurse.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Meronem can cause side effects, although not everybody gets them.

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data but this is rare or very rare).

Severe allergic reactions

If you have a severe allergic reaction, **stop having Meronem and see a doctor straight away**. You may need urgent medical treatment. The signs may include a sudden onset of:

- Severe rash, itching or hives on the skin.
- Swelling of the face, lips, tongue or other parts of the body.
- Shortness of breath, wheezing or trouble breathing.

Damage to red blood cells (not known)

The signs include:

- Being breathless when you do not expect it.
- Red or brown urine.

If you notice any of the above, **see a doctor straight away**.

Other possible side effects:

Common
- Abdominal (stomach) pain.
- Feeling sick (nausea).
- Being sick (vomiting).
- Diarrhoea.
- Headache.
- Skin rash, itchy skin.
- Pain and inflammation.
- Increased numbers of platelets in your blood (shown in a blood test).
- Changes in blood tests, including tests that show how well your liver is working.

Uncommon
- Changes in your blood. These include reduced numbers of platelets (which may make you bruise more easily), increased numbers of some white blood cells, decreased numbers of other white cells and increased amounts of a substance called 'bilirubin'. Your doctor may do blood tests from time to time.
- Changes in blood tests, including tests that show how well your kidney is working.
- A tingling feeling (pins and needles).
- Infections of the mouth or the vagina that are caused by a fungus (thrush).

Rare
- Fits (convulsions).

Other possible side effects of unknown frequency
- Inflammation of the bowel with diarrhoea.
- Sore veins where Meronem is injected.
- Other changes in your blood. The symptoms include frequent infections, high temperature and sore throat. Your doctor may do blood tests from time to time.
- Sudden onset of a severe rash or blistering or peeling skin. This may be associated with a high fever and joint pains.

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 nurse.

5. HOW TO STORE MERONEM

Keep out of the reach and sight of children.

Do not use Meronem after the expiry date which is stated on the container. The expiry date refers to the last day of that month.

Do not store above 30°C

After reconstitution: The reconstituted solutions for intravenous injection or infusion should be used immediately. The time interval between the beginning of reconstitution and the end of intravenous injection or infusion should not exceed one hour.

Do not freeze the reconstituted solution

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 Meronem contains

Each vial contains meropenem trihydrate equivalent to 500 mg anhydrous meropenem.

Each vial contains meropenem trihydrate equivalent to 1 g anhydrous meropenem.

The other ingredient is anhydrous sodium carbonate

What Meronem looks like and contents of the pack

- Meronem is a white to light yellow powder for solution for injection or infusion in vial. Pack sizes of 1 or 10 vials.

Marketing Authorisation Holder and Manufacturer
[See Annex I - To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:
Austria: Optinem
Belgium: Meronem IV
Bulgaria: Meronem
Cyprus: MERONEM
Czech Republic: MERONEM
Denmark: MERONEM
Estonia: Meronem
Finland: Meronem
France: MERONEM
Germany: Meronem
Greece: Meronem
Hungary: Meronem
Iceland: Meronem
Ireland: Meronem IV
Italy: MERREM
Latvia: Meronem
Lithuania: Meronem IV
Luxembourg: Meronem IV
Malta: Meronem IV
Netherlands: Meronem i.v.
Norway: Meronem
Poland: Meronem
Portugal: Meronem
Romania: Meronem i.v.
Slovak Republic: Meronem 500mg i.v.
Slovenia: Meronem
Spain: Meronem I.V.
Sweden: Meronem
United Kingdom: Meronem IV

This leaflet was last approved in {MM/YYYY}.
[To be completed nationally]

Advice/medical education

Antibiotics are used to treat infections caused by bacteria. They have no effect against infections caused by viruses.

Sometimes an infection caused by bacteria does not respond to a course of an antibiotic. One of the commonest reasons for this to occur is because the bacteria causing the infection are resistant to the antibiotic that is being taken. This means that they can survive and even multiply despite the antibiotic.

Bacteria can become resistant to antibiotics for many reasons. Using antibiotics carefully can help to reduce the chance of bacteria becoming resistant to them.

When your doctor prescribes a course of an antibiotic it is intended to treat only your current illness. Paying attention to the following advice will help prevent the emergence of resistant bacteria that could stop the antibiotic working.

1. It is very important that you take the antibiotic at the right dose, at the right times and for the right number of days. Read the instructions on the label and if you do not understand anything ask your doctor or pharmacist to explain.
2. You should not take an antibiotic unless it has been prescribed specifically for you and you should use it only to treat the infection for which it was prescribed.
3. You should not take antibiotics that have been prescribed for other people even if they had an infection that was similar to yours.
4. You should not give antibiotics that were prescribed for you to other people.
5. If you have any antibiotic left over when you have taken the course as directed by your doctor you should take the remainder to a pharmacy for appropriate disposal.

[To be completed nationally]

The following information is intended for medical or healthcare professionals only:

Instructions for giving Meronem to yourself or someone else at home
Some patients, parents and carers are trained to give Meronem at home.

Warning – You should only give this medicine to yourself or someone else at home after a doctor or nurse has trained you.

- The medicine must be mixed with another liquid (the diluent). Your doctor will tell you how much of the diluent to use.
- Use the medicine straight after preparing it. Do not freeze it.

How to prepare this medicine

1. Wash your hands and dry them very well. Prepare a clean working area.
2. Remove the Meronem bottle (vial) from the packaging. Check the vial and the expiry date. Check that the vial is intact and has not been damaged.
3. Remove the coloured cap and clean the grey rubber stopper with an alcohol wipe. Allow the rubber stopper to dry.
4. Connect a new sterile needle to a new sterile syringe, without touching the ends.
5. Draw up the recommended amount of sterile 'Water for Injections' into the syringe. The amount of liquid that you need is shown in the table below:

Dose of Meronem	Amount of 'Water for Injections' needed for dilution
500 mg (milligrams)	10 ml (milliliters)
1 g (gram)	20 ml
1.5 g	30 ml
2 g	40 ml

Please note: If your prescribed dose of Meronem is more than 1g, you will need to use more than 1 vial of Meronem. You can then draw the liquid in the vials into the one syringe.

6. Put the needle of the syringe through the centre of the grey rubber stopper and inject the recommended amount of Water for Injections into the vial or vials of Meronem.
7. Remove the needle from the vial and shake the vial well for about 5 seconds, or until all the powder has dissolved. Clean the grey rubber stopper once more with a new alcohol wipe and allow the rubber stopper to dry.
8. With the plunger of the syringe pushed fully into the syringe, put the needle back through the grey rubber stopper. You must then hold both the syringe and the vial and turn the vial upside down.
9. Keeping the end of the needle in the liquid, pull back the plunger and draw all the liquid in the vial into the syringe.
10. Remove the needle and syringe from the vial and throw the empty vial away in a safe place.
11. Hold the syringe upright, with the needle pointing upwards. Tap the syringe so that any bubbles in the liquid rise to the top of the syringe.
12. Remove any air in the syringe by gently pushing the plunger until all the air has gone.
13. If you are using Meronem at home, dispose of any needles and infusion lines that you have used in an appropriate way. If your doctor decides to stop your treatment, dispose of any unused Meronem in an appropriate way.

Giving the injection

You can either give this medicine through a short cannula or venflon, or through a port or central line.

Giving Meronem through a short cannula or venflon

1. Remove the needle from the syringe and throw the needle away carefully in your sharps bin.
2. Wipe the end of the short cannula or venflon with an alcohol wipe and allow it to dry. Open the cap on your cannula and connect the syringe.
3. Slowly push the plunger of the syringe to give the antibiotic steadily over about 5 minutes.
4. Once you have finished giving the antibiotic and the syringe is empty, remove the syringe and use a flush as recommended by your doctor or nurse.
5. Close the cap of your cannula and carefully throw the syringe away in your sharps bin.

Giving Meronem through a port or central line

1. Remove the cap on the port or line, clean the end of the line with an alcohol wipe and allow it to dry.
2. Connect the syringe and slowly push the plunger on the syringe to give the antibiotic steadily over about 5 minutes.
3. Once you have finished giving the antibiotic, remove the syringe and use a flush as recommended by your doctor or nurse.
4. Place a new clean cap on your central line and carefully throw the syringe away in your sharps bin.

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATIONS

The National Competent Authorities, coordinated by the Reference Member State, shall ensure that the following conditions are fulfilled by the Marketing Authorisation Holders:

The MAH commits to carrying out a number of quality-related steps pertaining to the Drug Substance and the Drug Product and to submit the data listed in the Letter of Undertaking within the specified timeframe. Where the data results in a variation, an application for a variation will be submitted to the RMS.