Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT (FPP)

MERONIA® 1000 IV
Meropenem

1.1. **Strength** 1000 mg
1.2. Pharmaceutical form Powder for solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains meropenem trihydrate equivalent to 1000 mg meropenem.

Excipients with known effect
Each vial contains 208 mg sodium carbonate equivalent to approximately 4 mEq of sodium (approximately 90 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

White to light yellow powder

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Meronia is indicated for the treatment of the following infections in adults and children aged 3 months and older (see sections 4.4 and 5.1).

- Severe pneumonia, including hospital and ventilator-associated 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

Meronia may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.
Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2. Posology and mode of administration

4.2.1. Posology

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 2000 mg 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 infections due to less susceptible bacterial species (e.g. *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Acinetobacter* spp.), or very severe infections.

Adults and adolescents

Infection	**"Unit dose" to be administered every 8 hours**
Severe pneumonia including hospital and ventilator-associated pneumonia	500 mg or 1000 mg
Broncho-pulmonary infections in cystic fibrosis	2000 mg
Complicated urinary tract infections	500 mg or 1000 mg
Complicated intra-abdominal infections	500 mg or 1000 mg
Intra- and post-partum infections	500 mg or 1000 mg
Complicated skin and soft tissue infections	500 mg or 1000 mg
Acute bacterial meningitis	2000 mg
Management of febrile neutropenic patients	1000 mg

- There are limited safety data available to support the administration of a 2000 mg dose in adults as an intravenous bolus injection.

4.2.2. Special populations

Renal impairment

The dose for adults and adolescents should be adjusted when creatinine clearance is less than 51 ml/min, as shown below.

Creatinine clearance (ml/min)	**Dose based on the "unit dose" in the table for adults here above in section 4.2.1**	**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

- There are limited data to support the administration of these dose adjustments for a unit dose of 2000 mg.
- Meropenem is cleared by haemodialysis and hemofiltration. 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.

Elderly patients

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

4.2.3. Pediatric 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.

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	**"Unit dose" to be administered every 8 hours**
Severe pneumonia including hospital and ventilator-associated 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.

4.2.4. Method of administration

- Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes.
- Alternatively, meropenem doses of up to 1000 mg or 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 2000 mg dose in adults and a 40 mg/kg dose in children as an intravenous bolus injection.
- For instruction for reconstitution of the powder before administration, see section 6.6.

4.3. Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1
- Hypersensitivity to any other carbapenem antibacterial agent.
- Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins or cephalosporins).

4.4. Special warning and precautions for use

4.4.1. General information

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.

Bacterial resistance

Resistance to penems of *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter* spp. varies. Prescribers are advised to take into account the local prevalence of resistance in these bacteria to penems.

Hypersensitivity reactions

- 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.
- Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme (EM) and acute generalised exanthematous pustulosis (AGEP) have been reported in patients receiving meropenem. If signs and symptoms suggestive of these reactions appear, meropenem should be withdrawn immediately and an alternative treatment should be considered.

Antibiotic-associated colitis

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. 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

Seizures have infrequently been reported during treatment with carbapenems, including meropenem.

Hepatic function monitoring

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

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.

Direct antiglobulin test (Coombs test) seroconversion
A positive direct or indirect Coombs test may develop during treatment with meropenem.

Valproic acid/sodium valproate/valpromide
The concomitant use of meropenem and valproic acid/sodium valproate/valpromide is not recommended.

Sodium
This medecine contains 90 mg of sodium per vial of Meronia 1000 IV, or 4.5% of the maximum daily dose recommended by the WHO (2g) for an adult.

4.4.2. Pediatric population

See section 4.4.1

4.5. Interactions with other medicinal products and other forms of interactions

Probenecid
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.

Valproic acid
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/sodium valproate/valpromide with carbapenem agents is not considered to be manageable and therefore should be avoided.

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.

Pediatric population

Interaction studies have only been performed in adults.

4.6. Fertility, pregnancy and lactation

4.6.1. Fertility

No data available

4.6.2. Pregnancy

There are limited data from the use of meropenem in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of meropenem during pregnancy.

4.6.3. Lactation

Small amounts of meropenem have been reported to be excreted in human milk. Meropenem should not be used in breast-feeding women unless the potential benefit for the mother justifies the potential risk to the baby.

4.7. Effects on the ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. However, when driving or operating machines, it should be taken into account that headache, paraesthesia and convulsions have been reported for meropenem.

4.8. Undesirable effects

Summary of the safety profile

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%).

Tabulated summary of adverse reaction

The frequencies of adverse reactions reported with meropenem are defined as:

- 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)
- not known (cannot be estimated from the available data)

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, agranulocytosis, haemolytic anaemia
Immune system disorders	Uncommon	angioedema, anaphylaxis
Nervous system disorders	Common	headache
	Uncommon	paraesthesia
	Rare	convulsions
Gastrointestinal disorders	Common	diarrhoea, vomiting, nausea, abdominal pain
	Uncommon	antibiotic-associated colitis
Hepatobiliary disorders	Common	transaminases increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased
	Uncommon	blood bilirubin increased
Skin and subcutaneous tissue disorders	Common	rash, pruritus
	Uncommon	urticaria, toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme
	Not known	drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis
Renal and urinary disorders	Uncommon	blood creatinine increased, blood urea increased
General disorders and administration site conditions	Common	inflammation, pain
	Uncommon	thrombophlebitis, pain at the injection site

Pediatric population

Meropenem is approved for administration in children from 3 months. There was no evidence of an increased risk of adverse events in children based on the limited data available. All reported cases were consistent with events observed in adults.

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 and ATC code**:** antibacterials for systemic use,

carbapenems, ATC code: J01DH02

Mechanism 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:

- decreased permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins),
- reduced affinity of the target PBPs,
- increased expression of efflux pump components,
- production of beta-lactamases that can hydrolyse carbapenems.

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 antibacterial agents when the mechanism involved include permeability 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 (2013-02-11, v 3.1)

Organism	**Susceptible (S) (mg/l)**	**Resistant (R) (mg/l)**
Enterobacteriaceae	≤ 2	> 8
Pseudomonas spp.	≤ 2	> 8
Acinetobacter spp.	≤ 2	> 8
Streptococcus groups A, B, C and G	note (6)	note (6)
Streptococcus pneumoniae (1)	≤ 2	> 2
Viridans group streptococci (2)	≤ 2	> 2
Enterococcus spp.	note (7)	note (7)
Staphylococcus spp.	note (3)	note (3)
Haemophilus influenza (1) (2) and *Moraxella catarrhalis* (2)	≤ 2	> 2
Neisseria meningitides (2) (4)	≤ 0.25	> 0.25
Gram-positive anaerobes except *Clostridium difficile*	≤ 2	> 8
Gram-negative anaerobes	≤ 2	> 8
Listeria monocytogenes	≤ 0.25	> 0.25
Non-species related breakpoints (5)	≤ 2	> 8

(1) Meropenem breakpoints for *Streptococcus pneumoniae* and *Haemophilus influenza* in meningitis are 0.25 mg/l (Susceptible) and 1 mg/l (Resistant).

(2) Isolates with MIC values above the susceptible breakpoint are very 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 values above the current resistant breakpoint they should be reported resistant.

(3) Susceptibility of staphylococci to carbapenems is inferred from the cefoxitin susceptibility.

(4) Breakpoints relate to meningitis only.
(5) Non-species related breakpoints have been determined using PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints. Non species related breakpoints are based on the following dosages: EUCAST breakpoints apply to meropenem 1000 mg x 3 daily administered intravenously over 30 minutes as the lowest dose. 2 g x 3 daily was taken into consideration for severe infections and in setting the I/R breakpoint.
(6) The beta-lactam susceptibility of streptococcus groups A, B, C and G is inferred from the penicillin susceptibility.
(7) Susceptibility testing not recommended as the species is a poor target for therapy with the drug. Isolates may be reported as R without prior testing.

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	**Gram-negative aerobes**
Enterococcus faecalis (S) *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)	*Citrobacter freundii* *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	**Gram-negative anaerobes**

Gram-positive aerobes	**Gram-negative aerobes**
Clostridium perfringens *Peptoniphilus asaccharolyticus* *Peptostreptococcus* species (including *P. micros, P anaerobius, P. magnus*)	*Bacteroides caccae* *Bacteroides fragilis* group *Prevotella bivia* *Prevotella disiens*

Species for which acquired resistance may be a problem

Gram-positive aerobes	**Gram-negative aerobes**
Enterococcus faecium (S) (R)	*Acinetobacter* species *Burkholderia cepacia* *Pseudomonas aeruginosa*

Inherently resistant organisms

Other micro-organisms	**Gram-negative aerobes**
Chlamydophila pneumoniae *Chlamydophila psittaci* *Coxiella burnetii* *Mycoplasma pneumoniae*	*Stenotrophomonas maltophilia* *Legionella* species

(S) Species that show natural intermediate susceptibility

(*) All methicillin-resistant staphylococci are resistant to meropenem

(R) Resistance rate ≥ 50% in one or more EU countries.

Glanders and melioidosis: Use of meropenem in humans is based on in vitro *B. mallei* and *B. pseudomallei* susceptibility data and on limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of glanders and melioidosis.

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 bi-exponential 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.

Biotransformation
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. Meropenem is cleared by haemodialysis with clearance during haemodialysis being approximately 4 times higher than 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.

Paediatric population
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.

5.3. Preclinical safety data

The IV LD50 of meropenem in rodents is greater than 2000 mg/kg.

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. 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 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

Sodium carbonate

6.2. Incompatibilities

Meronia should not be mixed with other medicinal products except those mentioned in section 6.6.

6.3. Shelf life

4 years

Following reconstitution

Each vial is for single use. From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbiological contamination, the product should be used immediately.

It is recommended to use freshly prepared solutions of Meronia® for IV injection and infusion.

If not used immediately in-use storage times and conditions are the responsibility of the user.

6.4. Special precautions for storage

Store below 30°C.

Reconstitution: shake the solution before use. The constituted solution should not be frozen.

6.5. Nature and contents of container

Meronia 1000 IV: 1348 mg powder corresponding to 1000 mg meropenem, filled in a colourless glass vial (type III) of 20 ml, closed with a grey rubber stopper and sealed with an aluminium cap with a plastic flip-top cover (colour light-grey) (sterile product).
Box with 1 vial.

6.6. Special precautions for disposal and other handlings

Each vial should be used only once and the remainder of the solution should be discarded.
Any unused product or waste material should be disposed of in accordance with local requirements.

Handling

Use standard aseptic techniques for the preparation and administration of the solution.

Intravenous bolus injection administration
A solution for bolus injection is prepared by dissolving the drug product in water for injections to a final concentration of 50 mg/ml. Shake the solution before use.
Chemical and physical in-use stability for a prepared solution for bolus injection has been demonstrated for 3 hours at up to 25°C or 12 hours under refrigerated conditions (2-8°C).
From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbiological contamination, the product should be used immediately.
If not used immediately in-use storage times and conditions are the responsibility of the user.

Intravenous infusion administration
A solution for infusion is prepared by dissolving the drug product in either 0.9% sodium chloride solution for infusion or 5% dextrose solution for infusion to a final concentration of 1 to 20 mg/ml.

Chemical and physical in-use stability for a prepared solution for infusion using 0.9% sodium chloride solution has been demonstrated for 3 hours at up to 25°C or 24 hours under refrigerated conditions (2-8°C).
From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbiological contamination, the product should be used immediately.
If not used immediately in-use storage times and conditions are the responsibility of the user.
Reconstituted solution of the product in 5% dextrose should be used immediately.
The constituted solution should not be frozen.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS

7.1. Marketing Authorisation Holder

Dafra Pharma GmbH, Mühlenberg 7, 4052 Basel, Switzerland.

7.2. Manufacturer

Anfarm Hellas S.A
61st km. Nat. Rd. Athens, Lamia, Schimatari Viotias, 32009, Greece

8. MARKETING AUHORISATION NUMBER

See list of MAs per country

9. DATE OF FIRST REGISTRATION

See list of MAs per country

10. PRODUCT SUPPLY CATEGORY

Prescription Only Medicine (POM)

11. DATE OF REVISION OF TEXT

03/2023