MEROPENEM / ANFARM 500 MG

MEROPENEM / ANFARM 1G

1. NAME OF THE MEDICINAL PRODUCT

Meropenem/ANFARM 500mg

Meropenem/ANFARM 1g

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Meropenem/ANFARM 500mg

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

Excipients with known effect:

Each 500 mg vial contains 104 mg sodium carbonate which equates to approximately 2 mEqof sodium (approximately 45 mg).

Meropenem/ANFARM 1 g
Each vial contains meropenem trihydrate equivalent to 1 g anhydrous meropenem.

Excipients with known effect:

Each 1 g vial contains 208 mg sodium carbonate which equates 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.

A white to light yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Meropenem/ANFARM IV is indicated for treatment, in adults and children, of the following infections caused by single or multiple bacteria sensitive to meropenem.

- Pneumonias and Nosocomial Pneumonias
- Pulmonary infections in patients with cystic fibrosis
- Urinary Tract Infections
- Intra-abdominal Infections
- Gynaecological Infections, such as endometritis and pelvic inflammatory disease
- Skin and Skin Structure Infections
- Meningitis
- Septicemia

Meropenem/ANFARM has proved efficacious alone or in combination with other antimicrobial agents inthe treatment of polymicrobial infections.

There is no experience in pediatric patients with neutropenia or primary or secondary immunodeficiency.

4.2 Posology and method of administration

Adults
The dosage and duration of therapy shall be established depending on type and severity of infection and the condition of the patient.

The recommended daily dosage is as follows:

500 mg IV every 8 hours in the treatment of pneumonia, UTI, gynaecological infections such as endometritis, pelvic inflammatory disease, skin and skin structure infections.

1 g IV every 8 hours in the treatment of nosocomial pneumonias, peritonitis, presumed infections in neutropenic patients, septicemia.

In cystic fibrosis, doses up to 2 g every 8 hours have been used; most patients have been treated with 2 g every 8 hours.

In meningitis the recommended dosage is 2 g every 8 hours.

> When treating infections known or suspected to be caused by Pseudomonas aeruginosa, a dose of at least 1g every 8 hours in adults (maximum approved dose is 6g daily given in 3 divided doses) and a dose of at least 20mg/kg every 8 hours in children (maximum approved dose is 120mg/kg/ daily given in 3 divided doses) are recommended.

Regular sensitivity testing is recommended when treating Pseudomonas aeruginosa infection.
There are limited safety data available to support the administration of a 2g bolus dose in adults as an intravenous bolus injection

Dosage Schedule for Adults with Impaired Renal Function

Dosage should be reduced in patients with creatinine clearance less than 51 mL/min, as scheduled below.

Table 1

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

Meropenem is cleared by haemodialysis and haemofiltration; if continued treatment with Meropenem/ANFARM is necessary, it is recommended that the unit dose (based on the type and severity of infection) is administered at the completion of the haemodialysis procedure to restore therapeutically effective plasma concentrations.
There is no experience with the use of Meropenem/ANFARM in patients under peritoneal dialysis.

Dosage in Adults with Hepatic Insufficiency
No dosage adjustment is necessary in patients with hepatic insufficiency (see Section 4.4).

Elderly Patients
No dosage adjustment is required for the elderly with normal renal function or creatinine clearance values above 50 mL/min.

Children
For children over 3 months and up to 12 years of age the recommended dose is 10 to 20 mg/kg every 8 hours depending on type and severity of infection, susceptibility of the pathogen and the condition of the patient. In children over 50 kg weight, adult dosage should be used. In meningitis and cystic fibrosis the recommended dose is 40 mg/kg every 8 hours.
There is no experience in children with renal impairment.

Method of Administration
Meropenem/ANFARM IV can be given as an intravenous bolus injection over approximately 5 minutes or by intravenous infusion over approximately 15 to 30 minutes using the specific available presentations. There is limited safety data available to support the administration of a 40mg/kg bolus dose (in children). There is limited safety data available to support the administration of a 2g bolus dose (in adults).

Meropenem/ANFARM IV to be used for bolus intravenous injection should be constituted with sterile Water for Injections (5 mL per 250 mg meropenem). This provides an approximate concentration of 50 mg/mL. Constituted solutions are clear, and colourless or pale yellow.

Meropenem/ANFARM IV for intravenous infusion may be constituted with compatible infusion fluids (50 to 200 ml) (see Sections 6.2 and 6.3 6.6).
Meropenem/ANFARM should not be mixed with or physically added to solutions containing other drugs.Solutions of Meropenem/ANFARM should not be frozen.

4.3 Contraindications

Hypersensitivity to the active substance 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 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 ofthe infection, the prevalence of resistance to other suitable antibacterial agents and the risk of selecting for carbapenem-resistant bacteria.

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

Hypersensitivity reactions
As with all beta-lactam antibiotics, serious and occasionally fatal hypersensitivity reactionshave 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 tobeta-lactam antibiotics.

If a severe allergic reaction occurs, the medicinal product should be discontinued andappropriate 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 (see section 4.8). If signs and symptoms suggestive of these reactions appear, meropenem should be withdrawn immediatelyand 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 (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 shouldnot be given.

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

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) (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).

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

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

Meropenem/ANFARM contains sodium.

Meropenem/ANFARM 500 mg: This medicinal product contains 45 mg sodium per 500 mg vial, equivalentto 2.25% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Meropenem/ANFARM 1 g: This medicinal product contains 90 mg sodium per 1 g vial, equivalent to 4.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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 interactionswith 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/sodium valproate/valpromide with carbapenem agents is not considered to be manageableand 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 bemonitored frequently during and shortly after co-administration of antibiotics with an oral anti-coagulant agent.

Paediatric population
Interaction studies have only been performed in adults.

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 reproductivetoxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of meropenem during pregnancy.

Breast-feeding
Small amounts of meropenem have been reported to be excreted in human milk. Meropenemshould 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 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, paresthesia 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 risk of adverse reactions
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); 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	agranulocytosis, haemolytic anaemia, thrombocytopenia, neutropenia, leukopenia, eosinophilia
Immune system disorders	Uncommon	anaphylaxis (see sections 4.3 and 4.4), angioedema
Psychiatric disorders	Rare	delirium
Nervous system disorders	Common	headache
	Uncommon	paresthesia
	Rare	convulsions (see section 4.4)
Gastrointestinal disorders	Common	diarrhoea, abdominal pain vomiting, nausea
	Uncommon	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, pruritus
	Uncommon	toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme. (see section 4.4), urticaria
	Not known	drug reaction with eosinophilia and systemic symptoms, acute generalised exanthematous pustulosis (see section 4.4)
Renal and urinary disorders	Uncommon	blood creatinine increased, blood urea increased

Table 1

System Organ Class	Frequency	Event
General disorders and administration site conditions	Common	inflammation, pain
	Uncommon	thrombophlebitis, pain at the injection site

Paediatric population

Meropenem/ANFARM is licensed for children over 3 months of age. There is no evidence of an increasedrisk of any adverse drug reaction in children based on the limited available data. All reports received were consistent with events observed in the adult population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.Any suspected adverse event should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

Relative overdose may be possible in patients with renal impairment if the dose is not adjustedas 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

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: (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 antibacterial 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 (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.	--	--
Staphylococcus spp.	note 3	note 3
Haemophilus influenzae[1, 2] *and Moraxella catarrhalis*[2]	≤ 2	> 2
*Neisseria meningitidis*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 breakpoints5	≤ 2	> 8

Organism	Susceptible (S) (mg/l)	Resistant (R) (mg/l)

[1] Meropenem breakpoints for *Streptococcus pneumoniae* and *Haemophilus influenzae* 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 identificationand 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 isolateswith 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. Nonspecies 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 penicillinsusceptibility.
-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug. Isolates maybe reported as R without prior testing.

The prevalence of acquired resistance may vary geographically and with time for selectedspecies 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 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
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.

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 multipledoses 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.

Biotransformation
Meropenem is metabolised by hydrolysis of the beta-lactam ring generating a microbiologically inactive metabolite. In vitro meropenem shows reduced susceptibility tohydrolysis 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), 5fold 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 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 adependence 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 meningitisare 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* in95% 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 inacute toxicity studies in rodent at doses exceeding 1000 mg/kg.

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

In repeat dose studies of up to 6 months duration only minor effects were seen including adecrease 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 andin monkeys up to 360 mg/kg.

There was no evidence of increased sensitivity to meropenem in juveniles compared to adultanimals. 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

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

After reconstitution:

Intravenous bolus injection administration

A solution for bolus injection is prepared by dissolving the drug product in water for injection to a final concentration of 50 mg/ml. Chemical and physical in-use stability for a prepared solution for bolus injection has been demonstrated for 2 hours at 25°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.

The constituted solutions should not be frozen.

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% glucose (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 4 hours at 25°C.

Constituted solutions of Meropenem/ANFARM IV in 5% glucose (dextrose) solution should be used immediately, i.e. within one hour following reconstitution.

The constituted solutions should not be frozen.

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.

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6.4 Special precautions for storage

Do not store above 25°C.

Protect from light.

Do not freeze the reconstituted solution.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Uncoloured glass vials type III having a capacity of 20 ml stoppered with bromobutyl rubber

stoppers having a diameter of 20 mm.

The medicinal product is supplied in pack size of 10 vials.

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. MANUFACTURER

ANFARM HELLAS S.A., 53-57, Perikleous Str., 153 44, Gerakas Attikis, Athens, Greece.

8. LICENSE HOLDER:

K.S. KIM INTERNATIONAL (SK-PHARMA) LTD., 94 Yigal Alon Str., Tel-Aviv-Yafo, 6789139.

9. LICENSE NUMBER:

Meropenem/ANFARM 500 mg: 150-53-33675

Meropenem/ANFARM 1g: 150-54-33679

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