

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Archifar 500 mg powder for solution for injection or infusion

Archifar 1g powder for solution for injection or infusion

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect: sodium.

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 the full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

A white to light yellow crystalline powder.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

Meropenem 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):

- 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.

Meropenem 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

### Posology

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

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

### *Adults and adolescents*

<b>Infection</b>	<b>Dose to be administered every 8 hours</b>
Severe pneumonia including hospital and ventilator-associated 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.

<b>Creatinine clearance (ml/min)</b>	<b>Dose</b> (based on “unit” dose range of 500 mg or 1g or 2g, see table above)	<b>Frequency</b>
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:

<b>Infection</b>	<b>Dose to be administered every 8 hours</b>
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.

#### Method of administration

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 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 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.

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

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 antibacterial 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/ valpromide is not recommended (see section 4.5).

#### **Archifar contains sodium.**

Archifar 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.

Archifar 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 Fertility, 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.

### Breast-feeding

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 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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  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, 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

System Organ Class	Frequency	Event
	Not known	Toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS Syndrome)
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

#### 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. Healthcare professionals are asked to report any suspected adverse reactions to Pharmaceutical Services, Ministry of Health, CY-1475, [www.moh.gov.cy](http://www.moh.gov.cy) / phs Fax: + 357 22608649.

#### **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

#### 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 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 (2013-02-11, v 3.1)**

<b>Organism</b>	<b>Susceptible (S) (mg/l)</b>	<b>Resistant (R) (mg/l)</b>
<i>Enterobacteriaceae</i>	$\leq 2$	$> 8$
<i>Pseudomonas spp.</i>	$\leq 2$	$> 8$
<i>Acinetobacter spp.</i>	$\leq 2$	$> 8$
<i>Streptococcus</i> groups A, B, C, and G	note 6	note 6
<i>Streptococcus pneumoniae</i> <sup>1</sup>	$\leq 2$	$> 2$
<i>Viridans group streptococci</i> <sup>2</sup>	$\leq 2$	$> 2$
<i>Enterococcus spp.</i>	--	--
<i>Staphylococcus spp.</i>	note 3	note 3
<i>Haemophilus influenzae</i> , <sup>1,2</sup> and <i>Moraxella catarrhalis</i> <sup>2</sup>	$\leq 2$	$> 2$
<i>Neisseria meningitidis</i> <sup>2,4</sup>	$\leq 0.25$	$> 0.25$
Gram-positive anaerobes except <i>Clostridium</i>	$\leq 2$	$> 8$

Organism	Susceptible (S) (mg/l)	Resistant (R) (mg/l)
<i>difficile</i>		
Gram-negative anaerobes	≤ 2	> 8
<i>Listeria monocytogenes</i>	≤ 0.25	> 0.25
Non-species related breakpoints <sup>5</sup>	≤ 2	> 8

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

<sup>2</sup>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 identification 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.

<sup>3</sup>Susceptibility of staphylococci to carbapenems is inferred from the ceftazidime susceptibility.

<sup>4</sup>Breakpoints relates to meningitis only.

<sup>5</sup>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.

The beta-lactam susceptibility of streptococcus groups A, B, C and G is inferred from the penicillin susceptibility.

-- = 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

*Enterococcus faecalis*<sup>S</sup>

*Staphylococcus aureus* (methicillin-susceptible)<sup>‡</sup>

*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*<sup>S†</sup>

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

<sup>§</sup>All methicillin-resistant staphylococci are resistant to meropenem

<sup>£</sup>Resistance rate  $\geq 50\%$  in one or more EU countries.

<sup>†</sup>Resistance rate  $\geq 50\%$  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**

### Absorption

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 C<sub>max</sub> 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 C<sub>max</sub> 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 C<sub>max</sub> 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 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 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.

### Paediatrics

The pharmacokinetics in infants and children with infection at doses of 10, 20 and 40 mg/kg showed C<sub>max</sub> 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 t<sub>1/2</sub> 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<sub>50</sub> 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 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**

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**

36 months.

In use stability: 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

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **6.5 Nature and contents of container**

Type I clear glass vials of 20ml and 30ml. Packs of 1, 10, 25, 50 and 100 vials are available.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal and other handling**

Standard aseptic technique should be employed during constitution. Shake constituted solution before use.

All vials are for single use only.

It is recommended to use freshly prepared solutions.

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

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

## **7. MARKETING AUTHORISATION HOLDER**

MEDOCHEMIE LTD, 1-10 Constantinoupoleos street, 3011 Limassol, Cyprus

## **8. MARKETING AUTHORISATION NUMBERS**

500mg: 20809

1g: 20810

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

500mg: 23/11/2010

1g: 24/11/2010

## **10. DATE OF REVISION OF THE TEXT**

06/2016