SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT(S)

Meropenem- Vit 500 mg
Meropenem- Vit 1 g

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Meropenem- Vit 500 mg
Each vial contains 570 mg meropenem trihydrate (sterile), equivalent to 500 mg anhydrous meropenem.
Excipient with known effect:
Each 500 mg vial contains 104 mg of sodium carbonate, corresponding to approximately 2.0 mEq of sodium (approximately 45 mg).

Meropenem- Vit 1 g
Each vial contains 1140 mg meropenem trihydrate (sterile), equivalent to 1000 mg anhydrous meropenem.
Excipient with known effect:
Each 1 g vial contains 208 mg of sodium carbonate, corresponding to approximately 4.0 mEq (approximately 90 mg).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion.
Vails containing white to light yellow powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Meropenem- Vit is indicated for the treatment in adults and children of the following severe infections caused by single or multiple susceptible bacteria sensitive to meropenem (see sections 4.4 and 5.1):

- Pneumonias and nosocomial pneumonias.
- Pulmonary infections in patients with cystic fibrosis.
- Urinary tract infections.
- Intra-abdominal infections.
- Gynecological infections such as endometritis and pelvic inflammatory disease.

- Skin and skin structure infections.
- Meningitis.
- Septicemia.

Meropenem- Vit has proved efficacious alone or in combination with other antimicrobial agents in the 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:

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

Meropenem- Vit 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 1 g every 8 hours in adults (maximum approved dose is 6 g daily given in 3 divided doses) and a dose of at least 20 mg/kg every 8 hours in children (maximum approved dose is 120 mg/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 2 g 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- Vit** 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- Vit** in patients under peritoneal dialysis.

Dosage in Adults with Hepatic Insufficiency
No dosage adjustment is necessary in patients with hepatic insufficiency (see section 5.2).

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- Vit is usually administered by intravenous infusion over approximately 15–30 minutes (see sections 6.2, 6.3 and 6.6). Alternatively, doses of up to 20 mg/kg of meropenem may be administered as an intravenous bolus over approximately 5 minutes There are limited safety data available to support the administration of 40 mg/kg dose in children as an intravenous bolus injection. There are limited safety data available to support the administration of a 2 g bolus dose in adults.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance (meropenem) 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 of the 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 . 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 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. 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 immediately and an alternative treatment should be considered.
With other beta-lactam antibiotics there have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction, see section 4.8).

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 should not be given.

Seizures
Seizures have infrequently been reported during treatment with carbapenems, including meropenem (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- Vit contains sodium.
Meropenem- Vit 500 mg: This medicinal product contains 45 mg sodium per 500 mg vial, equivalent to 2.25% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
Meropenem- Vit 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 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/ sodium valproate/ valpromide 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.

Paediatric population
Interaction studies have only been performed in adults.

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. 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 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 2

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, leucopenia, eosinophilia
Immune system disorders	Uncommon	anaphylaxis (see sections 4.3 and 4.4), angioedema
Psychiatric disorders	Rare	delirium
Nervous system disorders	Common	headache
	Uncommon	paraesthesia
	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
General disorders and administration site conditions	Common	inflammation, pain
	Uncommon	thrombophlebitis, pain at the injection site

Description of selected adverse reactions

Kounis Syndrome

Acute coronary syndrome associated with an allergic reaction (Kounis syndrome) has been reported with other beta-lactam antibiotics.

Paediatric population

Meropenem- Vit is licensed for children over 3 months of age. There is no evidence of an increased risk 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 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 antibacterial agents when the mechanism involved includes impermeability and/or an efflux pump(s).

Breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for meropenem, and are listed in table 3 below:

Table 3

Organisms	**Minimum Inhibitory Concentration (MIC) breakpoints (mg/L)**	
	Susceptible (S ≤)	**Resistant (R >)**
Achromobacter xylosoxidans	1	4
Acinetobacter spp. (indications other than meningitis)	2	8
Acinetobacter spp. (meningitis)	2	2
Aerococcus sanguinicola and A. urinae	0.25	0.25
Bacillus spp. except B. anthracis	0.25	0.25
Breakpoints for Bacteroides spp. are also valid for Parabacteroides spp. and for Phocaeicola dorei/vulgatus (previously named Bacteroides dorei/vulgatus).	1	1
Burkholderia pseudomallei	2	2
Clostridium perfringens	0.125[1]	0.125[1]
Corynebacterium diphtheriae and C. ulcerans	0.25[2]	0.25[2]
Cutibacterium acnes	0.125[1]	0.125[1]
Enterobacterales (indications other than meningitis)	2	8
Enterobacterales (meningitis)	2	2
Fusobacterium necrophorum	0.03[1]	0.03[1]
Haemophilus influenzae (indications other than meningitis)	2	2
Haemophilus influenzae (meningitis)	0.25	0.25

Kingella kingae	0.03	0.03
Listeria monocytogenes (all indications)	0.25	0.25
Moraxella catarrhalis	2	2
Neisseria gonorrhoeae	IE	IE
Neisseria meningitidis (all indications)	0.25	0.25
P. aeruginosa (indications other than meningitis)	2	8
P. aeruginosa (meningitis)	2	2
Prevotella spp.	0.25[1]	0.25[1]
Pseudomonas other than P. aeruginosa (indications other than meningitis)	2	8
Staphylococcus spp.	Note[3]	Note[3]
Streptococcus groups A, B, C and G	Note[4]	Note[4]
Streptococcus pneumoniae (indications other than meningitis)	2	2
Streptococcus pneumoniae (meningitis)	0.25	0.25
Vibrio spp.	0.5	0.5
Viridans group streptococci	2	2

[1] Isolates susceptible to benzylpenicillin can be reported susceptible to all beta-lactam agents with breakpoints (including those with Note) without further testing. Isolates resistant to benzylpenicillin should be tested for susceptibility to individual agents.

[2] Isolates "susceptible, increased exposure" (I) to benzylpenicillin can be reported susceptible to meropenem. Isolates resistant to benzylpenicillin should be tested for susceptibility to meropenem or reported resistant.

[3] Susceptibility of staphylococci to carbapenems is inferred from the cefoxitin susceptibility.

[4] The susceptibility of streptococcus groups A, B, C and G to carbapenems is inferred from the benzylpenicillin susceptibility.

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 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 C_{max} 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_{max} 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_{max} 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, gynecological 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.

Paediatric population
The pharmacokinetics in infants and children with infection at doses of 10, 20 and 40 mg/kg showed C_{max} 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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

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 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 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 (sterile).

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 3 hours at up to 25ºC or 12 hours under refrigerated conditions (2-8ºC).

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 25ºC or 24 hours under refrigerated conditions (2-8ºC).

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 solution should be used immediately.

The reconstituted solutions should not be frozen.

6.4 Special precautions for storage

Store below 25°C.
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

Meropenem- Vit 500 mg powder for solution for injection or infusion is packaged in a 20 ml type III colourless glass vial, with bromobutyl rubber stopper and violet coloured aluminum flip-off cap.

Meropenem- Vit 1 g powder for solution for injection or infusion is packaged in a 20 ml type III colourless glass vial, with bromobutyl rubber stopper and gray coloured aluminum flip-off cap.
The medicinal product is supplied in pack sizes 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% dextrose 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

ACS DOBFAR S.P.A.,
Viale Addetta, 4/12,
20067, Tribiano, Milano, Italy.

8 LICENSE HOLDER AND IMPORTER

Vitamed Pharmaceutical Industries Ltd.,
6 Hatachana St., P.O.BOX 114, Binyamina, 3055002, Israel.

9 MARKETING AUTHORISATION NUMBER(S)

Meropenem- Vit 500 mg: 178-44-37403-99

Meropenem- Vit 1 g: 178-45-37404-99

Revised in December 2025 according to MOH guidelines.