Product Specification

Galpen 1 gm

Packaging Component :1 g Vial+SWFI | **Pack Insert**

Developed on	: 8-1-13
Location	: Aquavitoe
Dimension	: L 107 mm x H 240 mm, Folding Size 107 x 30 mm
Item-code	: -
Pharma Code	: NA
Change Control No.	: NA
Barcode	: NA
Colours	: Black
Style	: Folded Insert (Front-Back Printing)
Substrate	: 54 gsm Maplitho paper
Previous AW No	: NA
Modified Date	: 6-2-15
Reason for revised AW	: New Art Work
Revision No.	: 5
Country	: Francophone
Designed by	: Selvakumar
Path	: Export/Francophone/Final French AW/Galpen 1g Inj

Colour

■ Black	-
-	-
-	-
-	-

Approval

QA/QC	Marketing	Production

Note : Before releasing of the artwork the above signature is a must.

Check Points	QA/QC	Markt.	Prod.	Check Points	QA/QC	Markt.	Prod.
Brand Name				Mkt. Add.			
Generic Name				Mfg.Lic.No.			
Pack/Grammage				Reg.No.			
Label Claim				OPZ Area			
Dosage				Item Code			
Storage				Dimensions			
Warnings				Colour			
Mfg. Add.				Barcode			

Front

Only for the use of the registered Medical Practitioner or a Hospital or a Laboratory

GALPEN

Meropenem for Injection USP 500 mg / 1 gm

COMPOSITION

MEROPENEM 500mg I.V. Injection
Each vial contains :
Meropenem Trihydrate U.S.P.
equivalent to Anhydrous
Meropenem 500 mg
Sodium Carbonate (Sodium 45.1 mg)

MEROPENEM 1gm I.V. Injection
Each vial contains: Meropenem Trihydrate U.S.P.
equivalent to Anhydrous
Meropenem 1000 mg Sodium Carbonate (Sodium 90.2 mg)

DESCRIPTION

MEROPENEM is a synthetic carbapenem antibiotic. Unlike imipenem, meropenem has a methyl group at position 1 of the 5-memberedring, which confers stability against hydrolysis by dehydropeptidase 1 (DHP 1) present on the brush border of proximal renal tubular cells and therefore does not require concomitant administraton with a DHP-1 inhibitor such as cilastatin. Chemically it is (4R,5S,6S)-3-[[(3S,5S)-5-(Dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate.

Chemical formula : $C_{17}H_{25}N_3O_5S \cdot 3H_2O$.
Molecular Weight (anhydrous): 437.5 (383.5)
MEROPENEM is commercially available as the trihydrate; potency is calculated on the anhydrous basis.

PHARMACOLOGY

MEROPENEM is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. Antibacterial action of MEROPENEM is related to binding of the drug to penicillin binding proteins (PBPs) of gram-positive and gram-negative organisms. The high resistance of meropenem to most bacterial β-lactamases and good penetration of the drug through the outer membrane also contribute significantly to antimicrobial activity. Meropenem may be less of an inducer of β-lactamases than imipenem.
High affinity of meropenem for PBPs 1, 2, and 4 of Staphylococcus aureus has been demonstrated. Against Escherichia coli, highest affinity is for PBP 2, although it also effectively binds to PBP 1a, 1b and 3; the affinity for PBP 3 is higher than imipenem in E. coli. The affinity of meropenem for PBPs 1b, 2 and 3 in Pseudomonas aeruginosa is higher than that of imipenem.

PHARMACOKINETICS

MEROPENEM is not absorbed when given orally and is normally administered by intravenous route. Peak plasma concentrations immediately after the completion of infusion are 50-60mg/lit after a 1g dose and 20-25mg/lit after 500mg. One hour after a 5 min infusion of 1g to healthy subjects average plasma concentrations are about 24mg/lit and decline to 0.7mg/lit at 6h. Steady-state plasma concentrations are achieved within 4h of commencing continuous infusion. At an infusion rate of 10mg/kg/6h the average steady-state concentration is 6.3mg/lit. There is no accumulation following intermittent infusion.
The pharmacokinetics is linear over the dose range 0.25-1.0g, the AUC increasing proportionately to dose, while there is no change in the half-life. The plasma half-life is approximately 1h, estimates for the mean varying from 0.9 to 1.2h. There is little inter-individual variation in the half-life with a standard of deviation of approximately 20% in most studies in healthy volunteers.
MEROPENEM is rapidly distributed throughout the body. The volume of distribution in humans is relatively low, only 0.3-0.4lit/kg. Approximately 25% of an intravenous dose of meropenem is converted to the antibacterially inactive ring-open form (ICI 213,689) by hydrolysis of the β-lactam ring, catalyzed by renal dehyropeptidase 1 (DHP-1). Meropenem is four times more resistant to human DHP-1 than imipenem. No other metabolite of meropenem is known. The metabolite is excreted essentially only via the kidneys. Upto 80% of a dose is excreted unchanged in the urine; the majority of the dose is excreted in the first 4h. Excretion in the feces is negligible. The total plasma clearance of meropenem is approximately 280ml/min of which renal clearance accounts for 75-80% (renal clearance 200ml/min).
The pharmacokinetics of MEROPENEM in children 1 year and older are very similar to those in adults with a half-life of approximately 0.8-1.1h. Upto 70% of the dose eliminated in the urine during the first 6h after dosing. The half-life was 2.95h in pre-term neonates and 2.04h in full term neonates. The half-life of MEROPENEM in elderly subjects with normal renal function for their age is approximately 50% longer than in young healthy adults.

MICROBIOLOGY

Meropenem shares the very broad antibacterial spectrum of imipenem. Clinically useful activity extends to the following types of bacteria; virtually all genera of the family Enterobacteriaceae; most aerobic and anaerobic Gram-positive cocci (Haemophilus spp., Neisseria spp., etc.); most isolates of Bacteroides fragilis and other anaerobic Gram-negative bacilli. In vitro meropenem exerts a greater activity than imipenem against Enterobacteriaceae (2 to 32 fold) and most pseudomonas (two to four fold) whereas it is slightly less active against Gram-positive species. Its activity against anaerobic Gram- negative rods is very similar to that of imipenem. Meropenem does not exhibit any useful activity against mycoplasmas, obligate intracellular bacteria such as chlamydiae and rickettsiae, and mycobacteria. Activity against Mycobacterium avium complex is known to be poor.

Table 1: Usual minimum inhibitory concentrations (MIC90S) of Meropenem for clinical isolates of common bacterial pathogens

Species	MIC90 (mg/L)
Gram-positive aerobes	
Enterococcus faecalis	6.0
E. faecium	64
Staphylococcus aureus (MS)	0.25
Staphylococcus aureus (MR)	32
Staphylococcus epidermidis	8
Streptococcus pneumoniae	
Penicillin sensitive	0.015
Penicillin resistant	2
Streptococcus pyogenes (Group A)	0.015
Streptococcus agalactiae (Group B)	0.06
Viridans streptococci	2
Listeria monocytogenes	2
Gram-negative aerobes	
Acinetobacter baumannii	2.0
Citrobacter freundii	0.06
C. koseri	<0.06
Enterobacter aerogenes	0.13
E. cloaceae	0.25
Escherichia coli	<0.06
Haemophilus influenzae	0.12
Klebsiella oxttoca	0.06
K. pneumoniae	0.06
Moraxella catarrhalis	0.12
Morganella morganii	0.25
Neisseriaspp.	0.03
Proteus mirabilis	0.25
P. vulgaris	0.25
Providencia rettgeri	0.25
P. stuartii	0.25
Pseudomonas aeruginosa	4.0
Serratia marcescens	0.25
Stenotrophomonas maltophilia	>64
Anaerobes	
Bacteroides fragilis	0.5
Clostridium perfringens	0.06
C. difficile	2.0
Peptostreptococcus anaerobius	0.25
Prevotella bivia	0.25
P. melaninogenica	0.13

INDICATIONS

GALPEN is indicated in the treatment of :
Nosocomial Pneumonia
Urinary Tract Infections
Intra Abdominal Infections
Gynaecological Infections
Skin and Skin tissue Infections
Meningitis
Septicaemia
Empiric Treatment of Adult Febrile Neutropenia
Culture and susceptibility testing should be performed where appropriate to determine the susceptibility of the causative microorganism(s) to meropenem.
Therapy with **GALPEN** may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

CONTRAINDICATIONS

GALPEN is contraindicated in patients who have shown immediate hypersensitivity reactions to penicillins or other β-lactam antibiotics.

WARNINGS

1. Hypersensitivity reactions
2. Pseudomembranous colitis

PRECAUTIONS

Seizure Potential
A tolerability concern with carbapenems is their potential to cause CNS toxicity and seizures. GALPEN appears to be associated with a risk of seizures, particularly in those with underlying CNS pathology. This risk is less than imipenem. In an overview of 46 clinical trials, which excluded patients with meningitis and a history of CNS disorders, the incidence of Meropenem related seizures was 0.08% of treatment exposures.

Drug Interactions
Probenecid competes with the renal tubular secretion of meropenem and increases the half-life by about one third.
Administration of meropenem to patients taking sodium valproate may result in the reduction of serum valproic acid levels. Subtherapeutic levels of valproic acid may be reached in some patients.

Interference with Laboratory Tests
No such interference has been reported.

Other Effects
A few cases of alterations in hematological values (including thrombocytopenia) and raised liver enzymes have been reported.

Usage in Pregnancy - Pregnancy Category B
There are no adequate and well-controlled studies of meropenem use in pregnant women and should be used during pregnancy only if clearly needed.

Nursing Mothers
It is not known whether meropenem is excreted in human breast milk. Caution should be exercised when GALPEN is administered to a nursing woman.

Paediatric Use
The safety and efficacy of GALPEN is in the treatment of meningitis has been established in patients only > 3 months of age.

In Elderly
No special problems yet evident. Renal excretion of meropenem and its ring-open metabolite are slowed in the elderly, in keeping with the decline of renal function, and the dosage interval should be reduced accordingly (See Dosage in renal impairment).

ADVERSE EFFECTS

Nausea, Vomitting Diarrhoea (antibiotic associated colitis reported), abdominal pain, disturbances in liver function tests; thrombocytopenia (reduction in partial thromboplastin time reported positive Coomb's Test, eosinophilia, leucopenia, neutropenia; headache, paraesthesia; hypersensitivity reactions including rash, pruritus, urticaria, angioedema, and anaphylaxis; also reported, convulsions Stevens-Johnson syndrome and toxic epidermal necrolysis; local reactions including pain and thrombophlebitis at injection site.

DOSAGE AND ADMINISTRATION

GALPEN is administered intravenously as a bolus injection given over 3-5 min. or by infusion over 15-30 min.
For Adults with normal renal function the usual dose is 0.5-1g every 8 hourly.
For the treatment of Adult meningitis, the dose is increased to 2g every 8 hourly. A dose of 10-20mg/kg every 8 hourly is recommended for children under 12 years.
In meningitis, the paediatric dose of 40mg/kg every 8 hourly is recommended
In children over 50 kg body weight the adult dosage should be given.

Dosage in Renal Impairment
In patients with impaired renal function (creatinine clearance < 50mL/min), the dose of meropenem should be adjusted to compensate for the slower rate of renal elimination.

TABLE 2: Recommended Maintenance Schedule in Adult Patients

Creatinine clearance (mL/min)	Recommended Maintenance Schedule		
> 50 Normal recommended dosing schedule	500 mg every 8h	1 g every 8h	2 g every 8h
	500 mg every 12h	1 g every 12h	2 g every 12h
	250 mg every 12h	500 mg every 12h	1 g every 12h
	250 mg every 12h	500 mg every 24h	1 g every 24h

When only serum creatinine is available, the following formula (Cockcroft and Gault equation) may be used to estimate creatinine.
Males :
Creatinine clearance (mL/min) =

$$\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females: 0.85 x Above value
No dosage guideline for meropenem is available in haemodialysis and peritoneal dialysis. Haemodialysis remove both meropenem and its metabolite (ICI 213,689) from plasma. It is therefore recommended that patients should be dosed after each haemodialysis session. The dialysis clearance of meropenem is 80ml/min.
No data is available about dosage adjustment in paediatric patients with renal impairment.

Dosage in hepatic impairment
Patients with hepatic impairment do not require adjustment of meropenem dosage.
Reconstitution of Single Dose Vials for Intravenous bolus/ Infusion Administration (Table 3).

Table 3: Reconstitution of GALPEN

GALPEN vial content added (mL)	Amount of Diluent to be
500 mg	10
1 g	20

The vial should be shaken until dissolution occurs and then allowed to stand until the solution is clear.
For intravenous bolus administration the resultant solution may then be injected over a 3-to 5-minute period.
For intravenous infusion, constitute the 500mg or 1g vial and dilute it with one of the compatible IV fluids to provide solutions containing approximately 2.5-50mg/mL (10-200mL for 500mg and 20-400mL for 1g) of the drug and should be infused IV over 15-30 minutes.

COMPATIBILITY AND STABILITY

Compatible fluids include 5% or 10% Dextrose, 0.9% Sodium chloride, 5% Dextrose and 0.9% or 0.225% Sodium chloride, 5% Dextrose and 0.15% Potassium chloride, 5% Dextrose and 0.02% Sodium bicarbonate, 2.5% or 10% Mannitol Solutions should be freshly prepared and used.
Meropenem constituted as directed is stable for 1-4hours at controlled room temperature 15°-25°C (59°-77°F) or for 2-24hrs at 4°C (39°F) depending on IV fluids used.
Stability is maximum for 0.9% Sodium chloride and Ringer's Lactate solution.

STORAGE

Store below 25°C in a dry place. Protect from light.
Keep out of reach of children.

240 mm

107 mm