DBL™ MEROPENEM FOR INJECTION

NAME OF MEDICINE
Meropenem Trihydrate

The chemical name of meropenem trihydrate is \(-\text{Azabicyclo}[3.2.0] \text{hept-2-ene-2- carboxylic acid, 3-} \left[5-\left(\text{dimethylamino}\right)\text{carbonyl}\text{-}3\text{-pyrrolidinyl}\text{-thio}\right]-6(1\text{-hydroxyethyl})\text{-}4\text{-methyl-7-oxo, trihydrate, } [4R-3(3S^*, 5S^*)\text{-}4\alpha, 5\beta, 6\beta (R^*)\text{-}]\left(4R, 5S, 6S\right)-3-\left[3(3S^*), 5S^*\right]-5(\text{Dimethyl carbamoyl})\text{-}3\text{-pyrrolidinyl}\text{-thio}\text{-}6\left(1R\right)-1\text{-hydroxyethyl}\text{-}4\text{-methyl-7-oxo-1- azabicyclo}[3.2.0] \text{hept-2-ene-carboxylic acid, trihydrate. The molecular formula of meropenem trihydrate is } C_{17}H_{25}N_{3}O_{5}S \cdot 3H_{2}O \text{ and its CAS number is } 119478-56-7.\)

The structural formula of meropenem trihydrate is shown below:-

![Structural formula of meropenem trihydrate]

DESCRIPTION
DBL™ Meropenem for Injection is presented as a sterile white powder containing meropenem trihydrate equivalent to meropenem, 500 mg or 1 g, blended with sodium carbonate anhydrous. DBL™ Meropenem for Injection contains 208 mg sodium carbonate anhydrous for each gram of meropenem (anhydrous potency). It contains no antimicrobial preservative and is for use in one patient on one occasion only.

<table>
<thead>
<tr>
<th>DBL™ Meropenem for Injection powder for intravenous injection or infusion</th>
<th>20mL</th>
<th>30mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEROPENEM trihydrate</td>
<td>570 mg</td>
<td>1.14 g</td>
</tr>
<tr>
<td>Equivalent to anhydrous meropenem</td>
<td>500 mg</td>
<td>1 g</td>
</tr>
<tr>
<td>Excipient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium carbonate anhydrous</td>
<td>104 mg</td>
<td>208 mg</td>
</tr>
</tbody>
</table>

PHARMACOLOGY
Meropenem is a carbapenem antibiotic for parenteral use, that is stable to human dehydropeptidase-1 (DHP-1).
Microbiology
Meropenem exerts its bactericidal action by interfering with vital bacterial cell wall synthesis. The ease with which it penetrates bacterial cell walls, its high level of stability to all serine β-lactamases and its marked affinity for the Penicillin Binding Proteins (PBPs) explain the potent bactericidal action of meropenem against a broad spectrum of aerobic and anaerobic bacteria. Bactericidal concentrations are commonly the same as the minimum inhibitory concentrations (MICs).

Meropenem is stable in susceptibility tests and these tests can be performed using normal routine methods. In vitro tests show that meropenem acts synergistically with various antibiotics. It has been demonstrated both in vitro and in vivo that meropenem has a post-antibiotic effect.

Meropenem is usually active, in vitro and in clinical infections, against the following strains of bacteria shown below:

**Gram-positive aerobes:** Enterococcus faecalis, Staphylococcus aureus (penicillinase negative and positive), Staphylococci-coagulase-negative including *Staphylococcus epidermidis*, streptococci including *Streptococcus pneumoniae*, *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Streptococcus mitis*, *Streptococcus milleri*, *Streptococcus sanguis*, *Streptococcus viridans*.


**Anaerobic bacteria:** Bacteroides fragilis, Bacteroides thetaiotaomicron, and other *Bacteroides* spp., *Clostridium* spp. including *C. perfringens*, *Eubacterium lentum*, *Fusobacterium* spp., *Mobiluncus curtisi*, Peptostreptococcus spp., Peptococcus spp.

Some strains of *Pseudomonas aeruginosa* are susceptible to meropenem in vitro and in clinical infections.

*Enterococcus faecium*, Stenotrophomonas (Xanthomonas) maltophilia, and methicillin resistant staphylococci have been found to be resistant to meropenem.

**Disc Susceptibility**
Dilution or diffusion techniques-either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method, (eg NCCLS).

Standard susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites.
where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable, other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Pharmacokinetics
A 30 minute intravenous infusion of a single dose of meropenem in normal volunteers results in peak plasma levels of approximately 11 microgram/mL for the 250 milligram dose, 23 microgram/mL for the 500 milligram dose, 49 microgram/mL for the 1 g dose and 115 microgram/mL following the 2 g dose.

A 5 minute intravenous bolus injection of meropenem in normal volunteers results in peak plasma levels of approximately 52 microgram/mL for the 500 mg dose and 112 microgram/mL for the 1g dose.

Intravenous infusions over two minutes, three minutes and five minutes of a 1g dose of meropenem were compared in a three-way crossover trial. These durations of infusion resulted in peak plasma levels of 110, 91 and 94 microgram/mL, respectively.

After an intravenous dose of 500 mg, plasma levels of meropenem decline to values of 1 microgram/mL or less than six hours after administration.

When multiple doses are administered at eight hourly intervals to subjects with normal renal function, accumulation of meropenem does not occur.

In subjects with normal renal function, meropenem's elimination half-life is approximately one hour.

Plasma protein binding of meropenem is approximately 2%.

Approximately 70% of the intravenous administered dose is recovered as unchanged meropenem in the urine over 12 hours, after which little further urinary excretion is detectable. Urinary concentrations of meropenem in excess of 10 microgram/mL are maintained for up to five hours at the 500 mg dose. No accumulation of meropenem in plasma or urine was observed with regimens using 500 mg administered every eight hours or 1g administered every six hours in volunteers with normal renal function.

The only metabolite of meropenem is microbiologically inactive.

Meropenem penetrates well into most body fluids and tissues including cerebrospinal fluid of patients with bacterial meningitis, achieving concentrations in excess of those required to inhibit most bacteria.

Studies in children have shown that the pharmacokinetics of meropenem in children are essentially similar to those in adults. The elimination half-life for meropenem was approximately 1.5 hours in children under the age of two years.
The pharmacokinetics are linear over the dose range of 10 to 40 mg/kg.

Pharmacokinetic studies in patients with renal insufficiency have shown the plasma clearance of meropenem correlates with creatinine clearance. Dosage adjustments are necessary in subjects with renal impairment.

Pharmacokinetic studies in the elderly have shown a reduction in plasma clearance of meropenem which correlated with age-associated reduction in creatinine clearance.

Pharmacokinetic studies in patients with liver disease have shown no effects of liver disease on the pharmacokinetics of meropenem.

**INDICATIONS**

DBL™ Meropenem for Injection is indicated for treatment of the following infections, in adults and children (aged 3 months and over), when the causative organisms are known or suspected to be resistant to commonly used antibiotics:

- Community acquired lower respiratory tract infection
- Hospital acquired lower respiratory tract infection
- Complicated urinary tract infection
- Febrile neutropenia
- Intra-abdominal and gynaecological (polymicrobial) infections
- Complicated skin and skin structure infections
- Meningitis
- Septicaemia

**CONTRAINDICATIONS**

DBL™ Meropenem for Injection is contraindicated in patients who have demonstrated hypersensitivity reactions to meropenem or other carbapenems, penicillins or other β-lactam antibiotics.

**PRECAUTIONS**

**Hypersensitivity reaction (allergic/anaphylaxis)**

Serious and occasionally fatal hypersensitivity reactions have been reported in patients receiving therapy with β-lactams. These reactions are more likely to occur in persons with a history of sensitivity to multiple allergens. There have been reports of patients with a history of penicillin hypersensitivity who have experienced severe hypersensitivity when treated with another β-lactam. Before initiating treatment with meropenem, careful inquiry should be made concerning previous hypersensitivity reactions to carbapenems, penicillins, or other β-lactam antibiotics. If an allergic reaction to meropenem occurs, discontinue the drug. Serious hypersensitivity reactions may require adrenaline and other emergency measures.

As with other β-lactam antibiotics, strains of *Pseudomonas aeruginosa* may develop resistance on treatment with meropenem. Development of resistance has been reported in pseudomonal hospital acquired lower respiratory tract infections. In such cases, meropenem should be used with caution and repeat sensitivity testing is recommended.
Gastrointestinal disease

**History of colitis:** Antibiotics should be prescribed with care for individuals with a history of gastrointestinal disease, especially ulcerative colitis, regional enteritis, or antibiotic associated colitis.

**Pseudomembranous colitis:** Pseudomembranous colitis has been observed with practically all antibiotics and may vary in severity from slight to life-threatening. It is important to consider the diagnosis of pseudomembranous colitis in the case of patients who develop diarrhoea when using an antibiotic. Although studies indicate that a toxin produced by *Clostridium difficile* is one of the main causes of antibiotic-associated colitis, other causes should be considered.

Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs that delay peristalsis, e.g. opiates and diphenoxylate with atropine e.g. Lomotil may prolong and/or worsen the condition and should not be used.

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

This medicinal product contains sodium which should be taken into consideration for patients on a controlled sodium diet.

**Use in Severe Meningitis**

Neurological sequelae were reported following treatment of severe meningitis with meropenem. In clinical trials these adverse events were reported in 23 of 148 patients treated with meropenem and in 17 of 144 patients treated with comparator antibiotics.

**Use in Patients with Renal Insufficiency**
(See DOSAGE AND ADMINISTRATION).

**Use in Patients with Liver Disease**
Hepatic function should be closely monitored during treatment with meropenem due to the risk of hepatic toxicity (hepatic dysfunction with cholestasis and cytosis). Patients with pre-existing liver disorders should have liver function monitored during treatment with DBL™ Meropenem for Injection.

**Carcinogenesis, Mutagenesis**
The carcinogenic potential of meropenem has not been investigated.

Meropenem, with and without metabolic activation as appropriate, was not genotoxic in assays for gene mutations (*Salmonella typhimurium*, *E. coli* and Chinese hamster ovary cells) and chromosomal damage (mouse micronucleus assay and human lymphocytes *in vitro*).
Impairment of Fertility
Fertility was not impaired in rats with exposures based on the area under the curve (AUC) slightly greater than those observed in patients at the recommended intravenous dose.

Use in Pregnancy (Category B2)
Reproduction studies conducted with meropenem in rats have shown no embryotoxicity or teratogenicity at plasma exposures (based on AUC values) approximately equal to those observed in patients at the recommended intravenous dose. In a teratology study in cynomolgus monkeys given daily intravenous injections meropenem showed no evidence of teratogenicity at dose levels up to 360 mg/kg/day.

There are however, no adequate or well controlled trials of meropenem in pregnant women.

Because reproduction studies are not always predictive of human response, DBL™ Meropenem for Injection should not be used in pregnancy unless the potential benefit justifies the potential risk to the foetus.

Australian categorisation definition of Category B2
Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

Use in Lactation
Meropenem has been reported to be excreted in human breast milk. DBL™ Meropenem for Injection should not be used in breast-feeding women unless the potential benefit justifies the potential risk to the baby.

Use in Children
Efficacy and tolerability in infants under 3 months of age have not been established; therefore, meropenem is not recommended for use below this age.

Effects on Laboratory Tests
A positive or indirect Coombs' test may develop.

Use with Valproic Acid/Sodium Valproate
The concomitant use of valproic acid/sodium valproate and DBL™ Meropenem for Injection is not recommended (see INTERACTIONS WITH OTHER MEDICINES)

Effects on ability to drive and use machines
No studies 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, paraesthesiae and convulsions have been reported for DBL™ Meropenem for Injection.
INTERACTIONS WITH OTHER MEDICINES
Meropenem has been administered concomitantly with many other medications without apparent adverse interaction. However, no specific medicine interaction studies other than with probenecid were conducted.

Probenecid
Probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem with the effect of increasing the elimination half-life and plasma concentration of meropenem. As the potency and duration of action of meropenem dosed without probenecid are adequate the co-administration of probenecid with meropenem is not recommended. The potential effect of meropenem on the protein binding of other drugs or metabolism has not been studied. However, the protein binding is so low (approximately 2%) that no interactions with other compounds would be expected on the basis of this mechanism.

Valproic acid/sodium valproate
A clinically significant reduction in serum valproic acid concentration has been reported in patients receiving carbapenem antibiotics resulting a 60-100% decrease valproic acid levels in about two days. Due to the rapid onset and the extent of the decrease, co-administration of DBL™ Meropenem for Injection in patients stabilised on valproic acid/sodium valproate is not considered to be manageable and therefore should be avoided (see PRECAUTIONS).

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

Oral anticoagulants
Simultaneous administration of antibiotics with warfarin may augment its anticoagulant effects. There have been many reports of increases in the anticoagulant effects of orally administered anticoagulant 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 normalized 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 anticoagulant agent.

ADVERSE EFFECTS
Meropenem is generally well tolerated. In clinical trials, adverse events lead to cessation of treatment in less than 1% of patients. Serious adverse events are rare.

Common Events
Local intravenous injection site reactions
Inflammation, thrombophlebitis, pain.

Gastrointestinal disorders
Nausea, vomiting, diarrhoea, abdominal pain.

Blood
Reversible thrombocythaemia.
Nervous system disorders
Headache

Skin and subcutaneous tissue disorders
Rash, pruritus, drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.

Liver function
Reversible increases in serum transaminases (alanine aminotransferase, aspartate aminotransferase), gammaglutamyltransferase, bilirubin, alkaline phosphatase and lactic dehydrogenase alone or in combination have been reported.

Uncommon events (< 1%) Systemic allergic reactions:
Systemic allergic reactions (hypersensitivity) may occur following administration of meropenem. These reactions may include angioedema and manifestations of anaphylaxis.

Skin and subcutaneous tissue disorder
Urticaria (uncommon). Severe skin reactions, such as erythema multiforme, Stevens-Johnson Syndrome and toxic epidermal necrolysis, have been observed.

Gastrointestinal disorders
Pseudomembranous colitis.

Hepatobiliary disorders
Jaundice and hepatic failure have been reported but a causal link with meropenem has not been established.

Blood and lymphatic system disorders
Uncommon - Eosinophilia, leucopenia, thrombocytopenia, and neutropenia. Rare - agranulocytosis; Very rare - haemolytic anaemia. A positive direct or indirect Coombs’ test may develop.

Cardiovascular
Cardiac failure has been reported but a causal link with meropenem has not been established.

Nervous system disorders
Uncommon - paraesthesiae. Rare – convulsions. Delirium, and hallucinations have been reported but a causal link with meropenem has not been established.

Respiratory
Pneumonia and respiratory failure have been reported but a causal link with meropenem has not been established.

Whole body
Fever and septicaemia have been reported but a causal link with meropenem has not been established.

Other
Oral and vaginal candidiasis, antibiotic-associated colitis.
DOSAGE AND ADMINISTRATION

Adults

*Usual dose:* 500 mg to 1 g of DBL™ Meropenem for Injection by intravenous administration every 8 hours depending on type and severity of infection, the known or suspected susceptibility of the pathogen(s) and the condition of the patient.

*Exceptions*
1. Febrile episodes in neutropenic patients - the dose should be 1g every 8 hours.
2. Meningitis - the dose should be 2g every 8 hours.

As with other antibiotics, caution may be required in using meropenem as monotherapy in critically ill patients with known or suspected *Pseudomonas aeruginosa* lower respiratory tract infection.

Regular sensitivity testing is recommended when treating *Pseudomonas aeruginosa* infection.

DBL™ Meropenem for Injection should be given as an intravenous bolus injection over approximately 5 minutes or by intravenous infusion over approximately 15 to 30 minutes (See *Method of Administration*). There is limited safety data available to support the administration of a 2 g bolus dose.

**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>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 to 50</td>
<td>one unit dose</td>
<td>every 12 hours</td>
</tr>
<tr>
<td>10 to 25</td>
<td>one-half unit dose</td>
<td>every 12 hours</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>one-half unit dose</td>
<td>every 24 hours</td>
</tr>
</tbody>
</table>

Meropenem is cleared by haemodialysis. If continued treatment with DBL™ Meropenem for Injection 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 peritoneal dialysis.

**Use in Adults with Hepatic Insufficiency**

No dosage adjustment is necessary in patients with impaired hepatic metabolism.

**Elderly Patients:**

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

**Children**

For infants and children over 3 months and up to 12 years of age the recommended intravenous dose is 10 to 40 mg/kg every 8 hours depending on type and severity of
infection, the known or suspected susceptibility of the pathogen(s) and the condition of the patient. In children over 50kg weight, adult dosage should be used.

**Exceptions:**

1. Febrile episodes in neutropenic patients - the dose should be 20 mg/kg every 8 hours.
2. Meningitis - the dose should be 40 mg/kg every 8 hours.

DBL™ Meropenem for Injection should be given as an intravenous bolus over approximately five minutes or by intravenous infusion over approximately 15 to 30 minutes. There is limited safety data available to support the administration of a 40 mg/kg bolus dose.

There is no experience in children with renal impairment.

**Method of Administration and Reconstitution**

DBL™ Meropenem for Injection to be used for bolus intravenous injection should be constituted with sterile Water for Injection (10 mL per 500 mg meropenem). This provides an approximate available concentration of 50 mg/mL. Reconstituted solutions are both clear and colourless to pale yellow.

DBL™ Meropenem for Injection to be used for intravenous infusion may be directly reconstituted with a compatible infusion fluid and then further diluted (50 to 200 mL) with the compatible infusion fluid.

Shake reconstituted solution before use. All vials are for single use in one patient only. Standard aseptic technique should be employed during constitution and administration.

**Compatibility**

DBL™ Meropenem for Injection is compatible with the following infusion fluids:

- 0.9% sodium chloride intravenous infusion
- 5% or 10% glucose intravenous infusion
- 5% glucose intravenous infusion with 0.02% sodium bicarbonate
- 0.9% sodium chloride and 5% glucose intravenous infusion
- 5% glucose with 0.225% sodium chloride intravenous infusion
- 5% glucose with 0.15% potassium chloride intravenous infusion
- 2.5% and 10% mannitol intravenous infusion
- normosol-M in 5% glucose intravenous infusion.

**Stability**

DBL™ Meropenem for Injection should not be mixed with or physically added to solutions containing other drugs.

To reduce microbiological hazard, solutions of DBL™ Meropenem for Injection should be used as soon as practicable after reconstitution. If storage is necessary, hold at 2 to 8°C for not more than 24 hours, or the period shown in the table below, whichever is the lesser.
Solutions of DBL™ Meropenem for Injection should not be frozen.

OVERDOSAGE
The pharmacological properties and mode of administration make it unlikely that intentional overdose will occur. Accidental overdosage could occur during therapy, particularly in patients with renal impairment. Treatment of overdosage should be symptomatic. In normal individuals rapid renal elimination will occur. In subjects with renal impairment haemodialysis will remove meropenem and its metabolite.

In case of overdose, immediately contact the Poisons Information Centre for advice (In Australia, call 13 11 26. In New Zealand call 0800 764 766).

PRESENTATION AND STORAGE CONDITIONS
DBL™ Meropenem for Injection packs contain 10 vials of meropenem trihydrate/sodium carbonate anhydrous blend as sterile powder:

20 mL vial – Meropenem trihydrate equivalent to meropenem 500 mg, sodium carbonate anhydrous 104 mg as buffer.

30 mL vial – Meropenem trihydrate equivalent to meropenem 1 g, sodium carbonate anhydrous 208 mg as buffer.

Prior to reconstitution, store DBL™ Meropenem for Injection packs below 25°C. See Compatibility and Stability for storage of prepared solutions.
NAME AND ADDRESS OF THE SPONSOR
Hospira NZ Limited
58 Richard Pearse Drive
Airport Oaks, Mangere 2022
Auckland
New Zealand

MEDICINE CLASSIFICATION
Prescription Medicine

DATE OF PREPARATION
18 February 2016