For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

This package insert is continually updated: Please read carefully before using a new pack

# ℞ Meropenem and Sulbactum for Injection Morenam SB 1.5 g

**For IV use only**

## Composition

Each vial Contains :
Meropenem Trihydrate ( Sterile) IP
equivalent to meropenem (Anhydrous) 1000 mg
Sodium Carbonate eq. to sodium
90.2 mg (as Buffer)
Sulbactam Sodium (Sterile) USP
eq. to Anhydrous Sulbactam 500 mg

**PHARMACEUTICAL FORM**

Morenam SB 1.5g (Meropenem and Sulbactam for Injection) 1.5 grams for injection, is supplied as a white to off-white sterile powder in single-dose vials containing 1 gram Meropenem and 0.5 gram Sulbactam.

**INDICATIONS**

Morenam SB 1.5g is indicated for treatment lower respiratory tract infection caused by gram negative bacteria in adults only. Meropenem has proved efficacious alone or in combination with other antimicrobial agents in the treatment of polymicrobial infections.

Intravenous Meropenem has been used effectively in patients with chronic lower respiratory tract infections, either as monotherapy or in combination with other antibacterial agents.

The presence of Sulbactam in the formulation effectively extends the antibiotic spectrum of Meropenem to include many bacteria normally resistant to it and to other beta-lactam antibiotics. Thus, the combination possesses the properties of a broad-spectrum antibiotics and a beta-lactamase inhibitor.

**DOSAGE**

Adults:
The dosage and duration of therapy shall be established depending on type and severity of infection and the condition of the patient. Dosage in based on Meropenem dosage.

The recommended daily dosage is as follows:

| Infection/Indication | Recommended Dose | Frequency | Route |
|---|---|---|---|
| Lower Respiratory Tract Infections | 1 g Meropenem / 0.5 g Sulbactam | Every 8 hours | Intravenous |

Renal impairment:
The dose for adults and adolescents should be adjusted when creatinine clearance is less than 51 ml/min, as shown below.

| Creatinine clearance (mL/min) | Dose Strength | Frequency |
|---|---|---|
| ≥51 | Recommended Dose | Every 8 hours |
| 26-50 | Recommended Dose | Every 12 hours |
| 10-25 | ½ of Recommended Dose | Every 12 hours |
| <10 | ½ of Recommended Dose | Every 24 hours |

Meropenem is cleared by hemodialysis and hemofiltration; if continued treatment with Meropenem is necessary, it is recommended that the unit dose (based on the type and severity of infection) be administered at the completion of the hemodialysis procedure to restore therapeutically effective plasma concentrations.

There is no experience with the use of Meropenem or the combination with Sulbactam in patients under peritoneal dialysis.

Dosage in Adults with Hepatic Insufficiency: No dosage adjustment is necessary in patients with hepatic insufficiency.

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

Children:
Since the combination has no data on the use in pediatric patients, use of this combination is not recommended.

Pregnancy Category B:
There are no adequate and well-controlled studies in pregnant Women. Meropenem and Sulbactam for injections should not be used in pregnancy unless the potential benefit justifies the risk of the foetus.

Pediatric population:
Since the combination has no data on the use in pediatric patients, use of this combination is not recommended.

There is no experience in children with renal impairment.

**METHOD OF ADMINISTRATION**

Standard aseptic techniques should be used for solution preparation and administration. Morenam SB 1.5g injection can be given as an intravenous bolus injection or as intravenous infusion. Intravenous infusion over approximately 15-30 minutes, using the specific available diluents.

*Intravenous bolus injection:*
For intravenous bolus injection, Morenam SB 1.5g can be reconstituted by dissolving the drug product in 20 mL sterile water for injection and given as intravenous bolus injection over approximately 3 to 5 minutes.

*Intravenous Infusion:*
For intravenous infusion, Morenam SB 1.5g vials may be directly constituted and diluted with 50 mL to 200 mL of either 0.9% sodium chloride solution for infusion or 5% dextrose solution and administered as intravenous infusion over approximately 15 to 30 minutes.

**AFTER RECONSTITUTION:**
Reconstituted solution of the product in 5% dextrose solution should be used immediately.
The constituted solutions should not be frozen.

Chemical and physical in-use stability for a prepared solution for bolus injection has been demonstrated for 3 hours at up to 25°C or 12 hours under refrigerated conditions (2-8°C).

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 25°C or 24 hours under refrigerated conditions (2-8°C). From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbiological contamination, the product should be used immediately.

If not used immediately in-use storage times and conditions are the responsibility of the user.

**COMPATIBILITY:**
Compatibility of Morenam SB 1.5g with other drugs has not been established. Morenam SB 1.5g should not be mixed with or physically added to solutions containing other drugs.

**INCOMPATIBILITIES:**
Morenam SB 1.5g should not be mixed with other medicinal products except those mentioned under above

**CONTRAINDICATIONS:**
Morenam SB 1.5g is contraindicated in patients with known hypersensitivity to any component of this product or 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).

**WARNINGS AND PRECAUTIONS:**

**Hypersensitivity reactions:**
**As with all beta-lactam antibiotics, serious and occasionally fatal hypersensitivity reactions have been reported. 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. It is important to inquire about previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactams and other allergens before initiating therapy with meropenem/sulbactam. If a severe allergic reaction occurs, the Morenam SB 1.5 g should be discontinued and appropriate emergency measures should be taken immediately.**

Clostridium difficile associated diarrhea (CDAD):
As with all antibiotics, Clostridium difficile associated diarrhea (CDAD), has been reported with use meropenem/sulbactam, and may range in severity from mild diarrhea to fatal colitis.

Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C difficile. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy.
CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. Discontinuation of therapy with meropenem/sulbactam and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should be avoided.

Seizure potential:
Seizures and other adverse CNS events have infrequently been reported during treatment with meropenem in patients with brain lesions, history of seizures, bacterial meningitis and impaired renal function.

Close adherence to the recommended dosage regimens is advised in patients with seizure disorder along with anti-convulsant therapy. In patients with advance age and renal impairment, dosage adjustment is recommended.

If myoclonus, focal tremors or seizure occurs, neurological evaluation along with institution of anti-convulsant therapy should be done. The decision regarding meropenem/sulbactam dose reduction or discontinuation should be taken on the basis of potential benefits and risks of continuation of therapy.

Severe Cutaneous Adverse Reactions:
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 generalized exanthematous pustulosis (AGEP) have been reported in patients receiving meropenem/sulbactam. If signs and symptoms suggestive of these reactions appear, meropenem should be withdrawn immediately and an alternative treatment should be considered.

Renal impairment:
Thrombocytopenia has been observed but no clinical bleeding has been reported in patient with renal impairment.

In patients on hemodialysis or peritoneal dialysis, there is inadequate data available regarding use of meropenem/sulbactam.

Valproic acid/sodium valproate/valpromide:
Reduction 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.

Morenam SB 1.5g contains sodium:
Morenam SB 1.5g contains 90.2 mg (3.92 mEq) of sodium per 1.5 g vial which should be taken into consideration before administration in patients with conditions that may require sodium restriction, such as congestive heart failure, hypertension, and fluid retention.

Development of Drug-Resistance:
In absence of a proven or strongly suspected susceptible bacterial infection, or a prophylactic indication, prescribers are advised to take into account the local prevalence of resistance in these bacteria to penems as it may lead to development of drug-resistant bacteria.

Lab Tests:
Periodic assessment of organ system functions, including renal, hepatic and hematopoietic system is advisable during prolonged therapy as meropenem posess the characteristic low toxicity of beta-lactams.

Overgrowth of Non-susceptible bacteria:
Prolonged use of meropenem/sulbactam may result in overgrowth of non-susceptible organisms as with other broad-spectrum antibacterial drugs. Repeated evaluation of the patient is required and appropriate measures must be taken if super-infections occur during therapy with meropenem/sulbactam.

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. Co-administration of probenecid with meropenem/sulbactam is not recommended.

Patients with Neuromotor impairment:
Patients receiving meropenem/sulbactam, on outpatient basis may develop adverse events such as seizures, headaches and/or paresthesias that could interfere with mental alertness and /or cause motor impairment. Until it is reasonably well established that meropenem/sulbactam is well tolerated, patients are not advised to operate machinery or motorized vehicle.

**CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY**

Carcinogenesis:
Carcinogenesis studies have not been performed with meropenem/sulbactam.

Mutagenesis:
Genetic toxicity studies were performed with meropenem using the Chinese hamster ovary HGPRT assay, the bacterial reverse mutation test, the mouse mononucleus test, cultured human lymphocyte cyclogenic assay, and no evidence of mutagenic potential was found in any of these tests.

Impairment of Fertility:
There was no reproducible toxicity seen when reproductive studies were performed with meropenem. In animal cell (rats to doses up to 1000 mg/kg/day and cynomolgus monkeys at doses up to 300 mg/kg/day).

**DRUG-TO-DRUG INTERACTIONS:**

Valproic acid/sodium valproate/valpromide:
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 manageable and therefore should be avoided.

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.

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 Normalized Ratio) is difficult to assess. The INR should be monitored frequently during and shortly after co-administration with an oral anti-coagulant agent.

**PREGNANCY AND LACTATION:**

Pregnancy Category B:
There are no or limited amount of data from the use of meropenem/sulbactam in pregnant women. Animal studies on meropenem do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precaution, it is preferable to avoid the use of meropenem during pregnancy.

Lactation:
Small amounts of meropenem/sulbactam 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.

Pediatric use:
The safety and effectiveness of meropenem have been established for pediatric patients 3 months of age and older with complicated skin and skin structure infections and bacterial meningitis, and for pediatric patients of all ages with complicated intra-abdominal infections.

Geriatric Use:
Meropenem is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with renal impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

A pharmacokinetic study with Morenam SB 1.5g in elderly patients has shown a reduction in the plasma clearance of meropenem that correlates with age-associated reduction in creatinine clearance.

Patients with Renal Impairment:
Pharmacokinetic studies with Morenam SB 1.5g in patients with renal impairment have shown that the plasma clearance of meropenem correlates with creatinine clearance. Dosage adjustments are necessary in subjects with renal impairment (creatinine clearance 50 mL/min or less).

Meropenem IV is hemodialyzable. However, there is no information on the usefulness of hemodialysis to treat overdosage

**ADVERSE REACTIONS:**
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.

| Adverse Reactions | Frequency | Event |
|---|---|---|
| Infections and infestations | Uncommon | oral and vaginal candidiasis |
| Blood and lymphatic system disorders | Common | thrombocythaemia |
| | Uncommon | eosinophilia, neutropenia, leucopenia, haemolytic anaemia, thrombocytopenia, agranulocytosis |
| Immune system disorders | Uncommon | angioedema, anaphylaxis |
| Nervous system disorders | Common | headache |
| | Uncommon | paraesthesiae |
| | Rare | convulsions |
| Gastrointestinal disorders | Common | diarrhoea, vomiting, nausea, abdominal pain |
| | Uncommon | antibiotic-associated colitis |
| Hepatobiliary disorders | Common | Increased levels of transaminases, alkaline phosphatase, blood lactate dehydrogenase |
| | Uncommon | blood bilirubin increased |
| Skin and subcutaneous tissue disorders | Common | rash, pruritis |
| | Uncommon | urticaria, toxic epidermalnecrolysis, Stevens Johnson syndrome, erythema multiforme |
| | Not Known | Drug Reactions with Eosinophilia and Systemic Symptoms (DRESS Syndrome) |
| Renal and urinary disorders | Uncommon | Increased blood creatinine, increased blood urea |
| General disorders and administration site conditions | Common | inflammation, pain |
| | Uncommon | thrombophlebitis, pain at the injection site |

**OVERDOSE:**
Accidental overdose may be possible specially in patients with renal impairment if the dose is not adjusted. Treatment for overdose is usually symptomatic.

In individuals with normal renal function, rapid renal elimination will occur. Haemodialysis will remove meropenem and its metabolite.

**DRUG DESCRIPTION:**
Meropenem is a broad-spectrum carbapenem antibiotic. Meropenem for injection is a sterile, pyrogen-free, synthetic, carbapenem antibacterial drug for intravenous administration. Meropenem 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. Its empirical formula is $C_{17}H_{25}N_3O_5S{\cdot}3H_2O$ with a molecular weight of 437.52.

Sulbactam is a β-lactamase inhibitor. Sulbactam sodium is a derivative of the basic penicillin nucleus. Chemically, sulbactam sodium is sodium penicillinate sulfone; sodium (2S, 5R)-3,3-dimethyl-7-oxo-4-thia1-azabicyclo [3.2.0] heptane-2-carboxylate 4,4-dioxide. Its chemical formula is $C_8H_{10}NNaO_5S$ with a molecular weight of 255.22.

**PHARMACODYNAMICS:**
The bactericidal activity of Morenam SB 1.5 g results from the inhibition of cell wall synthesis. Morenam SB 1.5 g readily penetrates the cell wall of most Gram-positive and Gram-negative bacteria to reac penicillin-binding- protein (PBP) targets. Its strongest affinities are toward PBPs 2, 3 and 4 of Escherichia coli and Pseudomonas aeruginosa; and PBPs 1, 2 and 4 of Staphylococcus aureus.

Sulbactam is given in combination with β-lactam antibiotics to inhibit β-lactamase, an enzyme produced by bacteria that destroys the antibiotics. Sulbactam in the Meropenem and Sulbactam for Injection formulation effectively extends the antibiotic spectrum of Meropenem to include many bacteria normally resistant.

The percentage of time of a dosing interval that unbound plasma concentration of meropenem exceeds the meropenem minimum inhibitory concentration (MIC) against the infecting organism has been shown to best correlate with efficacy in animal and in vitro models of infection.

**ANTIMICROBIAL ACTIVITY**
Antimicrobial activity of meropenem/sulbactam has been shown to be active against most isolates of the following bacteria, both in vitro and in clinical infections:

Gram-positive bacteria:
*Enterococcus faecalis* (vancomycin-susceptible isolates only)
*Staphylococcus aureus* (methicillin-susceptible isolates only)
*Streptococcus agalactiae*
*Streptococcus pneumoniae* (penicillin-susceptible isolates only)
*Streptococcus pyogenes*
*Viridans group streptococci*

Gram-negative bacteria:
*Escherichia coli*
*Haemophilus influenzae*
*Klebsiella pneumoniae*
*Neisseria meningitidis*
*Proteus mirabilis*
*Pseudomonas aeruginosa*

Anaerobic bacteria:
*Bacteroides fragilis*
*Bacteroides thetaiotaomicron*
*Peptostreptococcus species*

Greater than 90% of the following microorganisms exhibit activity in vitro with a minimum inhibitory concentration (MIC) less than or equal to the meropenem-susceptible breakpoint for organisms of similar genus. The safety and effectiveness of meropenem in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

**PHARMACOKINETICS:**
Distribution: The plasma protein binding of meropenem is approximately 2%. After a single intravenous dose of meropenem, the highest mean concentrations of meropenem were found in tissues and fluids at 1 hour (0.5 hours to 1.5 hours)

Elimination: Approximately 70% of the intravenously administered dose is recovered as unchanged meropenem in the urine over 12 hours, after which little further urinary excretion is detectable.

Half-life:
Approximately 1 hour in adults and children 2 years of age and older with normal renal function. Approximately 1.5 hours in children 3 months to 2 years of age.

Metabolism: There is one metabolite of meropenem that is microbiologically inactive.

Excretion: 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. Fecal elimination represents only approximately 2% of the dose.

**STORAGE AND HANDLING**
Store below 25°C. Protect from light and moisture. Keep the medicine out of reach of children.

Each vial is for single use only.

Any unused product or waste material should be disposed of in accordance with local requirements.

**HOW SUPPLIED**
Single dose vial with 1.5 gram of sterile Morenam SB 1.5g (Meropenem and Sulbactam for Injection) powder for injection.

**NATURE AND SPECIFICATION OF CONTAINER**
30 mL clear glass vials sealed with a rubber stopper (not made with natural rubber latex) and an aluminum overseal.

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