PATRIOT Pharmaceuticals Corp.

MEROPENEM

Rx **NATRONEM®**

500 mg Powder for Injection (I.V.)

Antibacterial

FORMULATION

Each vial contains:

Meropenem (as trihydrate)..... 500 mg

PHARMACODYNAMICS

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).

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.

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 include impermeability and/or an efflux pump(s).

PHARMACOKINETICS

After intravenous injection of meropenem 0.5 and 1 g over 5 minutes, peak plasma concentrations of about 50 and 112 micrograms/mL respectively are attained. The same doses are infused over 30 minutes produce peak plasma concentrations of 23 and 49 micrograms/mL respectively.

Meropenem has a plasma elimination half-life of about 1 hour; this may be prolonged in patients with renal impairment and is also slightly prolonged in children. Meropenem is widely distributed into body tissues and fluids including the CSF and bile. It is about 2% bound to plasma proteins. It is more stable to renal dehydropeptidase I than imipenem and is mainly excreted in the urine by tubular secretion and glomerular filtration. About 70% of a dose is recovered unchanged in the urine over a period of 12-hour period and urinary concentrations above 10 micrograms/mL are maintained for up to 5 hours after a 500-mg dose. Meropenem is reported to have one metabolite (ICI-213689), which is inactive and excreted in the urine.

Meropenem is removed by hemodialysis.

INDICATION

1. Susceptible Strain

Staphylococcus species, Streptococcus species, Enterococcus, Branhamella catarrhalis, Escherichia coli, Citrobacter species, Enterobacter species, Klebsiella species, Serratia species, Proteus species, Pseudomonas species, Influenzae, Bacteroides species, Neisseria meningitidis.

2. Indications

-Septicemia

-Superficial suppurative disorder (phlegmone, lymphadenitis, perianal abscess)

-Surgical and orthopedic infection (osteomyelitis, arthritis, wound infection)

-Respiratory tract infection (pneumonia, circumtonsillar abscess, chronic bronchitis, bronchiectasis, secondary infection of chronic respiratory disease, pulmonary abscess, empyema)

-Urinary tract infection (nephropyelitis, complicated cystitis)

-Gynecological infection (adnexitis, intrauterine infection, pelvic cavity infection, pelvis cellulitis)

-Otorhinological infection (otitis media, nasosinusitis)

-Bacterial meningitis (children from 3 month)

-Febrile neutropenia

-Cystic fibrosis

DOSAGE AND ADMINISTRATION

1. Adults: 500 mg to 1 g, 2-3 times daily, I.V. Infusion over approximately 30 minutes.

-Nosocomial pneumonia, peritonitis, febrile neutropenia, septicemia: 1 g I.V. Every 8 hours.

-Cystic fibrosis, meningitis: 2 g I.V. Every 8 hours.

2. Children from 3 months to 12 years:

-Bacterial meningitis: 40 mg/kg I.V. every 8 hours over approximately 30 minutes depending on the type and severity of infection, the known or suspected susceptibility of the pathogen(s) and the condition of the patient.

DIRECTION FOR RECONSTITUTION

1. Meropenem for injection to be used for bolus I.V. Injection should be reconstituted with sterile water for injection. This provides an approximate available concentration of 50 mg/mL.

2. Meropenem for injection to be used for I.V. Infusion may be directly reconstituted with a compatible infusion fluid (0.9% sodium chloride solution, 5% glucose (dextrose) solution) and then further diluted with another compatible infusion fluid.

CONTRAINDICATIONS

1. Patients who have demonstrated hypersensitivity to this drug.
2. Patients who have been administered valproic acid/sodium valproate.

SPECIAL PRECAUTIONS

1. 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.
2. Patients who have a history of hypersensitivity to carbapenems, penicillins or other beta-lactam antibiotics may also be hypersensitivity to meropenem. Before initiating therapy with meropenem, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics.
3. If a severe allergic reaction occurs, the medicinal product should be discontinued and appropriate measures taken.
4. Patients with severe renal impairment.
5. Patients who have a history of epilepsy and CNS impairment. (Symptoms of CNS with seizures and decreased consciousness have infrequently been reported during treatment with meropenem)
6. Patients with severe hepatic impairment.
7. Elderly.

GENERAL PRECAUTIONS

1. As with other ß-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.
2. As with other antibiotics, caution may be required in using with meropenem as monotherapy with critically ill patients with known or suspected Pseudomonas aeruginosa lower respiratory tract infection.
3. Regular sensitivity testing is recommended when treating Pseudomonas aeruginosa infection.

4. Pseudomembranous colitis has been observed with practically all antibiotics may vary in severity from slight to life-threatening. Therefore, antibiotics should be prescribed with care for individuals with a history of gastrointestinal complaints, particularly colitis. It is important to consider the diagnosis of pseudomembranous in the case of patients who develop diarrhea 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 eg. oral antibiotic agents effective against Clostridium difficile should be considered.
5. Fluids, electrolyte and protein replacement should be provided when indicated. Drugs that delay peristalsis, e.g. opiates and diphenoxylate with atropine may prolong and or worsen the condition and should not be used.
6. Neurological sequelae were reported following treatment of severe meningitis with meropenem. In clinical trials, these adverse events were reported in 23 out of 148 patients treated with meropenem and in 17 of 144 patients treated with comparator antibiotics.
7. A positive or indirect Coombs' test may develop.
8. Patients with Liver Disease: Patients with preexisting liver disorder should have liver function monitored during treatment with meropenem for injection.

ADVERSE REACTION
Meropenem is generally well tolerated. In clinical trials, adverse events lead to cessation of treatment in <1% of patients. Serious adverse events are rare.
1. Common Events: Local IV injection Site Reactions: Inflammation, thrombophlebitis, pain.
2. Gastrointestinal Disorders: Nausea, vomiting, diarrhea
3. Hematologic: Reversible thrombocytopenia
4. Hepatic Function: Reversible increases in serum transaminases, bilirubin, alkaline phosphatase and lactic dehydrogenase alone or in combination have been reported.
5. 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.
6. Dermatologic: Rash, pruritus, urticaria, severe skin reactions e.g. erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis have been observed.
7. Gastrointestinal Disorders: Pseudomembranous colitis, jaundice and hepatic failure have been reported but a casual link with meropenem has not been established.
8. Blood and Lymphatic System Disorders: Eosinophilia, leukopenia, thrombocytopenia, neutropenia, agranulocytosis, hemolytic anemia has been observed very rarely. A positive direct or indirect Coombs' test may develop
9. Cardiovascular: Cardiac failure has been reported but a causal link with Meropenem has not been established.
10. Central Nervous System: Headache, paresthesia, delirium, hallucinations and convulsions has been reported but a causal link with meropenem has not been established.
11. Respiratory: Pneumonia and respiratory failure have been reported but a causal link with meropenem has not been established.
12. Body as a Whole: Fever and septicemia have been reported but a causal link with meropenem has not been established.
13. Others: Oral and vaginal candidiasis

INTERACTION WITH OTHER DRUGS
1. Probenecid compares 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. The co-administration of probenecid with meropenem is not recommended.
2. Decreases in blood levels of valproic acid has been reported when it is co-administered with carbapenem agents resulting in a 60-100% decrease in valproic acid level in about two days. Due to the rapid onset and extent of the decrease co-admistration of valproic acid with carbapenem agents is not considered to be manageable and therefore should be avoided.

USE IN PREGNANCY AND LACTATION
1. Pregnancy
There are no or limited amount of data from the use of meropenem in pregnant women. As a precautionary measure, it is preferable to avoid using meropenem during pregnancy.
2. Lactation
It is unknown wether meropenem is excreted in human milk. Meropenem is detectable at very low concentrations in animal breast milk. A decision must be made wether to discontinue breast-feeding or to discontinue/abstain from meropenem therapy taking into account the benefit of therapy for the woman.
Pediatric Use
Efficacy and tolerability in infants less than 3 months have not been established. Therefore, this drug is not recommended for use in children below this age.
Geriatric Use
No dose adjustment is required in elderly patients with normal renal function or creatinine clearance values more than 50 mL per minute.
Overdose
Relative overdose may be possible in patients with renal impairment if the dose is not adjusted. Limited post-marketing experience indicates that if adverse reactions occur following overdose, they are consistent with the adverse reaction profile which are generally mild in severity and resolve in withdrawal or dose reduction. Symptomatic treatment should be considered. In individuals with normal renal function, rapid renal elimination will occur. Hemodialysis will remove meropenem and its metabolite.
Effects on ability to drive and Use machines
No studies on the effect on the ability to drive and use machines have been performed.

CAUTION:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

STORAGE:
Store at temperatures not exceeding to 30°C.

AVAILABILITY: USP Type I glass vial (Box of 1's and 10's)

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