Bosch

For Medical Professional only

PENRO® Injection I.V.

(MEROPENEM)

Powder for Solution for Injection/Infusion

پین رو انجکشن

(میروپینم)

DESCRIPTION:

Penro (meropenem for injection) is a sterile, pyrogen-free, synthetic, carbapenem antibacterial for intravenous administration. It is (4R,5S,6S)-3-[[(3S,5S)-5-(Dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6-[(1R)-1-hydroxyethyl]-4methyl-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.

PENRO is a white to pale yellow crystalline powder. The solution varies from colorless to yellow depending on the concentration. Meropenem is soluble in 5% monobasic potassium phosphate solution, sparingly soluble in water, very slightly soluble in hydrated ethanol, and practically insoluble in acetone or ether.

COMPOSTION:

Penro 500mg Injection:

Each vial contains:

Meropenem U.S.P. 500mg
as Meropenem Trihydrate
Also contains 45.1mg of sodium as sodium carbonate
(Product Specs.: U.S.P.)

Penro 1000mg Injection:

Each vial contains:

Meropenem U.S.P. 1000mg
as Meropenem Trihydrate
Also contains 90.2mg of sodium as sodium carbonate
(Product Specs.: U.S.P.)

CLINICAL PHARMACOLOGY:

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).

Microbiology

Gram-positive aerobes:

- Enterococcus faecalis
- Staphylococcus aureus
- Streptococcus agalactiae
- Streptococcus pneumoniae
- Streptococcus pyogenes
- Viridans group streptococci
- Staphylococcus epidermidis

Gram-negative aerobes:

- Escherichia coli
- Haemophilus influenzae
- Klebsiella pneumoniae
- Neisseria meningitidis
- Proteus mirabilis
- Pseudomonas aeruginosa
- Aeromonas hydrophila
- Campylobacter jejuni
- Citrobacter freundii
- Citrobacter koseri
- Enterobacter cloacae
- Hafnia alvei
- Klebsiella oxytoca
- Moraxella catarrhalis
- Morganella morganii
- Pasteurella multocida
- Proteus vulgaris
- Serratia marcescens

Anaerobic bacteria:

- Bacteroides fragilis
- Bacteroides thetaiotaomicron
- Peptostreptococcus species
- Bacteroides ovatus
- Bacteroides uniformis
- Bacteroides ureolyticus
- Bacteroides vulgatus
- Clostridium difficile
- Clostridium perfringens
- Eggerthella lenta
- Fusobacterium species
- Parabacteroides distasonis
- Porphyromonas asaccharolytica
- Prevotella bivia
- Prevotella intermedia
- Prevotella melaninogenica
- Propionibacterium acnes

Pharmacokinetics:
The mean plasma half-life is approximately 1 hour; the mean volume of distribution is approximately 0.25 l-l/kg 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 Cmax values of approximately 23, 49 and 115 µg/ml respectively, corresponding AUC values were 39.3, 62.3 and 153 µ g.h/mL.
After infusion over 5 minutes Cmax 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.

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.

Metabolism
Meropenem is metabolised by hydrolysis of the beta-lactam ring generating a microbiologically inactive metabolite.

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.

Specific Populations
Renal insufficiency
Renal impairment results in higher plasma AUC and longer half-life for meropenem. 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.
Meropenem is cleared by haemodialysis with clearance during haemodialysis being approximately 4 times higher than in anuric patients.

Hepatic insufficiency
In patients with alcoholic cirrhosis shows no effect of liver disease on the pharmacokinetics of meropenem after repeated doses.

Pediatrics:
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.

Elderly:
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

Therapeutic Indications:
Meropenem Powder for Solution for injection or Infusion is indicated for the treatment of the following infections.
- Severe pneumonia, including hospital and ventilator-associated pneumonia
- Broncho-pulmonary infections in cystic fibrosis
- Complicated urinary tract infections
- Complicated intra-abdominal infections
- Intra- and post-partum infections
- Complicated skin and soft tissue infections
- Acute bacterial meningitis

Meropenem may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Dosage
A dose of up to 2 g three times daily in adults and adolescents and a dose of up to 40 mg/kg three times daily in children may be particularly appropriate when treating some types of infections, such as infections due to less susceptible bacterial species or very severe infections.
Additional considerations for dosing are needed when treating patients with renal insufficiency

Adults and Adolescents

Infection	Dose to be administered every 8 hours
Severe pneumonia including hospital and ventilator-associated pneumonia.	500 mg or 1 g
Broncho-pulmonary infections in cystic fibrosis	2 g
Complicated urinary tract infections	500 mg or 1 g
Complicated intra-abdominal infections	500 mg or 1 g
Intra- and post-partum infections	500 mg or 1 g
Complicated skin and soft tissue infections	500 mg or 1 g
Acute bacterial meningitis	2 g
Management of febrile neutropenic patients	1 g

Alternatively, doses up to 1 g can be given as an intravenous bolus injection over approximately 5 minutes.

Renal impairment
Dosage should be reduced in patients with creatinine clearance less than 51 mL/min, as scheduled below.

Creatinine Clearance (mL/min)	Dose (based on unit doses of 500mg, 1g & 2g)	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. The required dose should be administered after completion of the haemodialysis cycle.
There are no established dose recommendations for patients receiving peritoneal dialysis.

Hepatic impairment
No dosage adjustment is necessary in patients with hepatic impairment.

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

Paediatric population:
Children from 3 months to 11 years of age and up to 50 kg body weight
The recommended dose regimens are shown in the table below:

Infection	Dose to be administered every 8 hours
Severe pneumonia including hospital and ventilator-associated pneumonia	10 or 20 mg/kg
Broncho-pulmonary infections in cystic fibrosis	40 mg/kg
Complicated urinary tract infections	10 or 20 mg/kg
Complicated intra-abdominal infections	10 or 20 mg/kg
Complicated skin and soft tissue infections	10 or 20 mg/kg
Acute bacterial meningitis	40 mg/kg
Management of febrile neutropenic patients	20 mg/kg

Children over 50 kg body weight,
The adult dose should be administered.
There is no experience in children with renal impairment.

Pediatric Patients Less Than 3 Months of Age
For pediatric patients (with normal renal function) less than 3 months of age, with complicated intra-abdominal infections, PENRO dose is based on gestational age (GA) and postnatal age (PNA). PENRO should be given as intravenous infusion over 30 minutes.

Age Group	Dose (mg/kg)	Dose interval
Infants less than 32 weeks GA and PNA less than 2 weeks	20	Every 12 hours
Infants less than 32 weeks GA and PNA 2 weeks and older.	20	Every 8 hours
Infants 32 weeks and older GA and PNA less than 2 weeks	20	Every 8 hours
Infants 32 weeks older GA and PNA 2 weeks and older	30	Every 8 hours

Method Of Administration
Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes. Doses of 1 gram may also be administered as an intravenous bolus injection (5 mL to 20 mL) over approximately 3 minutes to 5 minutes.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Contraindications
Hypersensitivity to the active substance or to any of the excipients. Hypersensitivity to any other carbapenem antibacterial agent.
Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of betalactam antibacterial agent (e.g. penicillin or cephalosporin).

Warnings and Precautions
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.

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.
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. If signs and symptoms suggestive of these reactions appear, meropenem should be withdrawn immediately and an alternative treatment should be considered.

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. 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.

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).

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.

Meropenem contains sodium.
Meropenem 1.0 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.

Drug Interaction
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. Caution is required if probenecid is co-administered with meropenem.

Valproic Acid
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.

Oral Anti-coagulants
Simultaneous administration of antibiotics with warfarin may augment its anti-coagulant effects. It is recommended that the INR should be monitored frequently during and shortly after co-administration of antibiotics with an oral anti-coagulant agent.

USE IN PREGNANCY AND LACTATION:
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 the use of meropenem during pregnancy.

Lactation:
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.

Adverse effects
Common: Thrombocythaemia, Headache, diarrhea, vomiting, nausea, abdominal pain, transaminases increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, rash, pruritis, inflammation, pain.

Uncommon: Oral and vaginal candidiasis, eosinophilia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis, hemolytic anaemia, angioedema, anaphylaxis, Paraesthesia, antibiotic-associated colitis, blood bilirubin increased, urticaria, toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme, blood creatinine increased, blood urea increased, thrombophlebitis, pain at the injection site.

Rare: convulsions, Delirium.

Not known: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS Syndrome)

OVERDOSAGE:
Relative overdose may be possible in patients with renal impairment if the dose is not adjusted. Symptomatic treatments should be considered. In individuals with normal renal function, rapid renal elimination will occur. Hemodialysis will remove meropenem and its metabolite.

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 sodium chloride 9 mg/mL (0.9 %) solution for infusion or glucose 50 mg/mL (5%) solution for infusion, to a final concentration of 1 to 20 mg/mL.
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.
It is recommended to use freshly prepare solution of Penro for injection and infusion.

Reconsitution Direction
The reconstituted solutions for intravenous injection or infusion should be used immediately. The time interval between the beginning of reconstitution and the end of intravenous injection or infusion should not exceed one hour.
Re-constitute injection vials (10ml per 500 mg and 20ml per 1 gram) with sterile Water for Injection. Shake to dissolve and let stand until clear.

Instructions for use and handling
Standard aseptic technique should be employed during constitution.
Shake reconstituted solution before use. All vials are for single use only.

Shelf life
Penro has a shelf life of 3 years.

Storage and Instructions
Protect from heat, sunlight and moisture. store below 30°C.
The expiration date refer to the product correctly stored at the required condition.
Reconstituted product should be used immediately and must be stored for no longer than 24 hours under refrigeration, only if necessary. Not to be use if solution is not clear
Keep out of reach of children.
Patients and healthcare professionals can also report suspected adverse drug reaction at ade@bosch-pharma.com.
To be sold on prescription of a registered medical practitioner only.

Presentation:
Penro 500mg Injection: Pack of 1 vial + 1 Ampoule of 10ml water for injection.
Penro 1000mg Injection: Pack of 1 vial + 2 Ampoules of 10ml water for injection.

صرف وریدی استعمال کیلئے۔

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
دھوپ، گرمی اور نمی سے محفوظ ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
انجکشن میں کوئی غیر حل پذیر شے نظر آنے کی صورت میں ہرگز استعمال نہ کریں۔
تیار شدہ انجکشن فوری استعمال کرلیں، انتہائی ضرورت ہو تو ریفریجریٹر میں رکھیں ۲۴ گھنٹے بعد استعمال نہ کریں۔
بچوں کی پہنچ سے دُور رکھیں۔
صرف معتمد ڈاکٹر کے نسخے پر فروخت کریں۔

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