SUPRANEM®

(Imipenem / Cilastatin)

Description

Supranem® is a combination of imipenem monohydrate which is a systemic carbapenem β - lactam antibacterial, and cilastatine sodium, that prevents the renal metabolism of imipenem by dehydropeptidase I.

Ingredients:

It contains Imipenem monohydrate and cilastatin sodium as active ingredients, Sodium bicarbonate as excipient.

Clinical pharmacology

The imipenem component of Supranem® inhibits bacterial cell wall synthesis by binding to one or more of the penicillin binding proteins (PBPs) and so blocks the final transpeptidation of peptidoglycan synthesis in bacterial cell wall thus inhibiting cell wall biosynthesis. Bacteria eventually lyses due to ongoing activity of cell wall autolytic enzymes while cell wall assembly is arrested. The cilastatin component of Supranem® prevents renal metabolism of imipenem by competitive inhibition of dehydropeptidase of renal tubules.

Pharmacokinetics

Half-life	I.V.: 60 minutes
Distribution	Rapidly and widely to most tissues and fluids including sputum, pleural fluid, peritoneal fluid, interstitial fluid, bile, aqueous humor, and bone; highest concentrations in pleural fluid, interstitial fluid, and peritoneal fluid; low concentrations in CSF
Metabolism:	Renal
Excretion:	Urine (~ 70% unchanged drug)
Protein binding	Imipenem: 20%; cilastatine: 40%

Indication

Treatment of lower respiratory tracts, urinary tract, intra -abdominal, gynecologic, bone and joint, skin and skin structure and poly-microbic infections, bacterial septicemia and endocarditis. Antibacterial activity: resistant gram-negative bacilli *(Pseudomonas aeruginosa Enterobacter sp)*, gram-positive bacteria (methiciline-sensitive *Staphylococcus aureus* and *Streptococcus* sp) and anaerobes.

Contraindication

- Supranem® is contraindicated in patients with hypersensitivity to imipenem/cilastatin or any component of the formulation.
- Supranem® is contraindicated in patients with meningitis (safety and efficacy have not been established)

Precautions and Warnings

- Dosage adjustment is necessary in patient with impaired renal function
- Elderly patients often require lower doses (adjust to renal function)
- Prolonged use may cause fungal or bacterial super-infection, including *C. difficile*-associated diarrhea (observed >2 months postantibiotic treatment) and pseudomembranous colitis.
- As it has been associated with CNS adverse effects (e.g. confessional states and seizures), use with caution in patients with a history of seizures.
- Patients with impaired renal function are at increased risk of seizures if not properly dose adjusted.
- Not recommended in pediatric CNS infections due to seizure potential.
- I.V. use in newborns to 16-year old children with non-CNS infections is supported by evidence from adequate and well - controlled studies. It is not recommended in pediatric patients less than 30kg with impaired renal function as no data are available.
- Use with caution in patients with a history of hypersensitivity to beta-lactams (including penicillins and cephalosporins).
- Serious hypersensitivity reactions including anaphylaxis has been reported, some of them without a history of previous allergic reactions to beta-lactams.

Pregnancy

Pregnancy category C.

No human reproductive studies have been conducted. Some adverse events are observed in some animal studies, especially with large doses, but most of such studies have shown no risk. Volume of distribution and clearance are increased in pregnant women.

Breast feeding

Supranem® enters breast milk. Use with caution.

Dosage

NOTE: The dosage is based on imipenem content. The administration route is I.V.

Usual Dosage Ranges

- Neonates ≤ 3 months and weight ≥ 1500g-Non-CNS infections:
  <1 week: 25 mg/kg every 12 hours
  1-4 weeks: 25 mg/kg every 8 hours
  4 weeks to 3 months: 25 mg/kg every 6 hours
- Children > 3 months - non-CNS infections:
  15-25mg/kg every 6 hours; maximum dosage: susceptible infections: 2 g/day; moderately-susceptible organisms: 4g/day
- Adults:
  Weight ≥ 70 kg: 250-1000 mg every 6-8 hours; maximum 4g/day
  NOTE: For adults weighing <70 kg refer to Dosing adjustment in renal impairment

Cystic fibrosis

Children: Doses up to 90 mg/kg/day have been used

Intra-abdominal infections

Adults: Mild infections: 250-500 mg every 6 hours; Severe: 500 mg every 6 hours

Mild infections

NOTE: Rarely used for mild infections
Adults: Fully susceptible organisms: 250 mg every 6 hours; Moderately-susceptible organisms: 500 mg every 6 hours

Moderate infections

Adults: Fully susceptible organisms: 500mg every 6-8 hours; Moderately-susceptible organisms: 500 mg every 6 hours or 1 g every 8 hours

Severe infections

Adults: Fully susceptible organisms: 500 mg every 6 hours; Moderately-susceptible organisms: 1 g every 6-8 hours
NOTE: Maximum daily dose should not exceed 50 mg/kg or 4 g/day, whichever is lower

Urinary tract infections

Uncomplicated: 250 mg every 6 hours
Complicated: 500 mg every 6 hours

Liver abscess (unlabeled)

Adults: 500 mg every 6 hours for 2-3 weeks, then appropriate oral therapy for a total of 4-6 weeks

Neutropenic fever (unlabeled)

Adults: 500 mg every 6 hours

Pseudomonas infections

Adults: 500 mg every 6 hours
NOTE: Higher doses may be needed based on organism sensitivity.

Burkholderia Pseudomallei (melioidosis)(unlabeled)

- Children: 20 mg/kg every 8 hours for 10 days
- Adults 20 mg/kg(up to 1g) every 6-8 hours for 10 days

Dosing Adjustment in renal impairment

- Patients with a Clcr ≤ 5 ml/minute/1.73 m^2 should not receive Supranem® unless hemodialysis is instituted within 48 hours.
- Patients weighing <30 kg with impaired renal function should NOT receive Supranem®.
- Hemodialysis: Use the dosing recommendation for patients with a Clcr 6-20 ml/minute; administer dose after dialysis session and every 12 hours thereafter
- Peritoneal dialysis: Dose as for Clcr 6-20 ml/minute

Reduced I.V. Dosage Regimen Based on Creatinine Clearance (ml/minute/1.73 m2)

	Body Weight (kg)				
	≥ 70	60	50	40	30
Total daily dose for normal renal function : 1 g/day					
Clcr ≥ 71	250 mg q6h	250 mg q8h	125 mg q6h	125 mg q6h	125 mg q8h
Clcr 41-70	250 mg q8h	125 mg q6h	125 mg q6h	125 mg q8h	125 mg q8h
Clcr 21-40	250 mg q12h	250 mg q12h	125 mg q8h	125 mg q12h	125 mg q12h
Clcr 6-20	250 mg q12h	125 mg q12h	125 mg q12h	125 mg q12h	125 mg q12h
Total daily dose for normal renal function : 1,5 g/day					
Clcr ≥ 71	500 mg q8h	250 mg q6h	250 mg q6h	250 mg q8h	125 mg q6h
Clcr 41-70	250 mg q6h	250 q8h	250 mg q8h	125 mg q6h	125 mg q8h
Clcr 21-40	250 mg q8h	250 mg q8h	250 mg q12h	125 mg q8h	125 mg q8h
Clcr 6-20	250 mg q12h	250 mg q12h	250 mg q12h	125 mg q12h	125 mg q12h
Total daily dose for normal renal function : 2 g/day					
Clcr ≥ 71	500 mg q6h	500 mg q8h	250 mg q6h	250 mg q6h	250 mg q8h
Clcr 41-70	500 mg q8h	250 mg q6h	250 mg q6h	250 mg q8h	125 mg q6h
Clcr 21-40	250 mg q6h	250 mg q8h	250 mg q8h	250 mg q12h	125 mg q8h
Clcr 6-20	250 mg q12h	250 mg q12h	250 mg q12h	250 mg q12h	125 mg q12h
Total daily dose for normal renal function : 3 g/day					
Clcr ≥ 71	1000 mg q8h	750 mg q8h	500 mg q6h	500 mg q8h	250 mg q6h
Clcr 41-70	500 mg q6h	500 mg q8h	500 mg q8h	250 mg q6h	250 mg q8h
Clcr 21-40	500 mg q8h	500 mg q8h	250 mg q6h	250 mg q8h	250 mg q8h
Clcr 6-20	500 mg q12h	500 mg q12h	250 mg q12h	250 mg q12h	250 mg q12h
Total daily dose for normal renal function : 4 g/day					
Clcr ≥ 71	1000 mg q6h	1000 mg q8h	750 mg q8h	500 mg q6h	500 mg q8h
Clcr 41-70	750 mg q8h	750 mg q8h	500 mg q6h	500 mg q8h	250 mg q6h
Clcr 21-40	500 mg q6h	500 mg q8h	500 mg q8h	250 mg q6h	250 mg q8h
Clcr 6-20	500 mg q12h	500 mg q12h	500 mg q12h	250 mg q12h	250 mg q12h

Dosing Adjustment in hepatic impairment

Hepatic dysfunction may further impair cilastatin clearance, so consider decreasing the dosing frequency.

Administration

- Add 20 ml NaCl (0.9%) or dextrose (5%) solution to the vial and shake well. Add the resultant suspension to a vessel containing at least 100 ml of the same solution and shake well until the mixture turns into a clear solution. Administer this solution as I.V. infusion during 20-30 minutes.
- If the final solution is cloudy or if there is any particles, AVOID use.
- The color of the final solution must be clear to yellow. If it is brown, AVOID use.
- In case of nausea, reduce the speed of administration.
- In case of concomitant use with other antibiotics, do NOT mix them.
- Supranem® DO NOT INJECT BY DIRECT I.V. BOLUS.
- Do not use solvents containing benzyl alcohol for I.V. infusion for children.

Patient consultation

- In case of severe diarrhea, call your physician immediately.

- Do not take anti-diarrhea medications without prior consultation with your physician.
- Your urine output should decrease after use.
- Report itching, rash, hives, difficulty in breathing, black furry tongue, loose foul smelling stool and vaginal itching or discharge to your physician.
- Tell your physician if you have any sensitivities to any drugs foods.

Interaction

- Avoid concomitant use of Supranem® with any of the following: BCG; Ganciclovir; Ganciclovir Systemic
- The levels or effects of Supranem® may be increased by Ganciclovir; Ganciclovir Systemic; Uricosuric agents
- Supranem® may decrease the levels or effects of BCG, Divalproex, Typhoid Vaccine, Valproic Acid

Adverse reactions

Cardiovascular: Tachycardia
Central Nervous System: Seizure
Dermatologic: Rash
Gastrointestinal: Nausea, diarrhea, vomiting
Genitourinary: Oliguria/anuria
Local: Phlebitis/thrombophlebitis

Less common adverse reactions (limited to important or life threatening):

Abdominal pain, abnormal urinalysis, acute renal failure, alkaline phosphatase increased, anaphylaxis, anemia, angioneurotic edema, asthenia, bilirubin increased, bone marrow depression, BUN/creatinine increased, candidiasis, confusion, cyanosis, dizziness, drug fever, dyspnea, encephalopathy, eosinophilia, erythma multiforme, fever, flushing, gastroenteritis, glossitis, hallucinations, headache, hearing loss, hematocrit decreased, hemoglobin decreased, hemolytic anemia, hemorrhagic colitis, hepatitis (including fulminant onset), hepatic failure, hyperchloremia, hyperhidrosis, hyperkalemia, hypersensitivity, hyperventilation, hyponatremia, hypotension, injection site erythema, jaundice, lactate dehydrogenase increased, leukocytosis, leucopenia, myoclonus, neutropenia (including agranulocytosis), palpitation, pancytopenia, paresthesia, pharyngeal pain, polyarthralgia, polyuria, positive Coombs'test, prothrombin time increased, pruritus, pruritus vulvae, pseudomembranous colitis, psychic disturbances, rash, resistant *P.aeruginosa*, salivation increased, somnolence, staining of teeth, Stevens-Johnson syndrome, taste perversion, thoracic spine pain, thrombocytopenia, thrombocythemia, tinnitus, tongue/tooth discoloration, tongue papillar hypertrophy, toxic epidermal necrolysis, transaminases increased,tremor, urine discoloration, urticaria, vertigo

Overdose

Treat symptomatically and institute supportive measurements as required. Supranem® is hemodialysable. However its usefulness is questionable in overdosage setting.

Storage and stability condition

- Before reconstitution store below 30°C, protect from light and keep the vial in the package.
- Keep out of the reach of children.
- DO NOT use the drug after the expiration date
- Use the solution after reconstitution immediately.

Packaging

Vials for I.V. infusion: 250 mg and 500 mg

References:

- Drug Information Handbook (Lexicomp® Drug Reference Handbooks/ APhA®): 2010-2011, Pages: 784-787
- PDR 64: 2010
- A to Z Drug Facts: 6th edition, Pages: 1957-1960

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