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Sulbactam for Injection

MATABAC™ / MATABAC™ 2g

COMPOSITION

MATABAC™
Each vial contains
Sulbactam Sodium USP (sterile)
equivalent to Sulbactam 1000 mg.

MATABAC™ 2g
Each vial contains
Sulbactam Sodium USP (sterile)
equivalent to Sulbactam 2000mg

PHARMACEUTICAL FORM

Powder for injection.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties
Pharmacotherapeutic group: Beta-lactamase inhibitors

Mechanism of Action

Sulbactam is a penicillanic acid sulfone with beta-lactamase inhibitory properties. Sulbactam attaches to certain penicillin binding proteins (PBP) and increases the sensitivity of microbial species that are sensitive to antibiotics. Due to its binding to PBP, sulbactam has strong and clinically significant intrinsic antimicrobial activity against certain organisms, specifically *Acinetobacter and Bacteroides* species and also against *Gonococcus and Diplococcus intracellularis*. Clinical studies have demonstrated the efficacy of sulbactam alone in treatment of serious *Acinetobacter baumanni* infections including those resistant to carbapenams, aminoglycosides, and other beta-lactams. It also has a strong inhibitory effect against the Richmond type and lactamase, but is weak against type I lactamase. When co-administered with penicillins or cephalosporins, together they decrease the minimum inhibitory concentrations (MIC) of *Staphylococcus aureus, Hemophilus influenza, Escherichia coli, and Bacteroides fragilis,* which are tolerated with the above 2 types of antibiotics because of enzyme production into a sensitive range. The antimicrobial activity of sulbactam against certain selected organisms is displayed in the following table.

Antimicrobial Activity of Sulbactam Against Selected Organism

Organism	β-Lactamase[a]	MIC(μg/mL)[b]
Staphylococcus aureus	Penase	200
Klebsiella pneumoniae	Broad spectrum	50
Proteus morganii	Penase	100
Escherichia coli	Penase	200
	Cephase	50
Pseudomonas aeruginosa	Cephase	>400
Neisseria gonorrhoeae	Broad spectrum	1.2
Haemophilus influenzae	Broad spectrum	100
Bacteroides fragilis	Cephase	25

[a] Penase: penicillinase; broad spectrum: broad-spectrum substrate profile; Cephase: cephalosporinase;
[b] MIC determined at inoculums of 10^6 CFU.

Pharmacokinetic Properties

Sulbactam is poorly absorbed from the gastrointestinal (GI) tract and is given by injection as the sodium salt. The pharmacokinetics of parenteral sulbactam and ampicillin are found to be similar. Sulbactam is also given orally as the pivoxil derivative—pivsulbactam along with amoxicillin. In addition, sulbactam has also been given with cefoperazone. Ampicillin is an excellent partner of sulbactam considering the pharmacokinetics of the 2 products. When given as a single dose, neither component has any effect on the kinetics of the other. On completion of a 15 minute intravenous infusion of sulbactam, peak serum concentrations are attained. The peak serum levels attained range from 48 to 88 mcg/mL on administration of 1000 mg sulbactam and 21 to 40 mcg/mL after administration of 500 mg sulbactam. After an IM injection of 500 mg sulbactam, peak serum levels ranging from 6 to 24 mcg/mL are attained. The mean serum half life of is approximately 1 hour in healthy volunteers.

Absorption

As sulbactam sodium is not absorbed appreciably from the GI tract and must be given parenterally, peak serum concentrations of sulbactam are attained immediately following completion of a 15 minute IV infusion. Following an IM injection of sulbactam sodium, the drug is rapidly and almost completely absorbed and peak serum concentrations are attained within 30 to 52 minutes.

Peak serum concentrations and areas under the concentration-time curve (AUCs) of sulbactam are slightly higher in geriatric patients than in younger adults; this presumably occurs because of reduced renal clearance in the elderly.

In a study in neonates who received ampicillin sodium and sulbactam sodium in a 1:1 ratio (50 mg/kg of each drug) given every 12 hours by rapid IV injection, plasma concentrations of ampicillin at 3, 8, and 12 hours averaged 86.8, 77.3, and 56.8 mcg/mL, respectively; and those of sulbactam at the same intervals averaged 110.2, 72.8, and 38.4 mcg/mL, respectively. There is no evidence that sulbactam accumulates in serum following an IM or IV administration of 0.5 g every 6 hours for 3 days in adults with normal renal function.

Distribution

Sulbactam sodium is well distributed into fluids and tissues following an IM or IV administration. Although sulbactam is distributed into certain tissues and fluids (eg, blister fluid, peritoneal fluid, intestinal mucosa) to a larger extent than ampicillin, the distribution of sulbactam may vary and may appear to depend on the extent of local inflammation. Sulbactam is found in peritoneal fluid, blister fluid, tissue fluid, sputum, middle ear effusion, intestinal mucosa, bronchial wall, alveolar lining fluid, sternum, pericardium, myocardium, endocardium, prostate, gallbladder, bile, myometrium, salpinges, ovaries, and the appendix. Concentrations of the drugs in most of these tissues and fluids generally are 53% to 100% of concurrent serum concentrations. Sulbactam readily crosses the placenta and concentrations in the umbilical cord blood were found to be similar to serum concentrations. Sulbactam is distributed in milk in low concentrations. On receiving 500-mg or 1-g of sulbactam by IV infusion over 20 minutes every 6 hours, in lactating women, concentrations of the drug in milk averaged 0.52 mcg/mL in samples obtained at random intervals between the first and the thirteenth doses.

Elimination

Serum concentrations of sulbactam decline in a biphasic manner. The major route of elimination of sulbactam is glomerular filtration and tubular secretion. Only small amounts of the drugs are eliminated in feces and bile.

Preclinical Safety Data

Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

CLINICAL PARTICULARS

Therapeutic Indications

MATABAC™ / MATABAC™ 2g vial including IM/IV injectable powder is a beta lactamase inhibitor that is used in treatment of severe bacterial infections in combination with certain antibiotics. Clinical studies have shown the efficacy of sulbactam alone in the treatment of serious *Acinetobacter baumannii* infections including those resistant to carbapenems.

Posology and Method of Administration

Sulbactam for injection may be administered by either the IV or the IM routes.The recommended dose is 500 to 1000 mg sulbactam every 6, 8, or 12 hours for adults, when administered in combination with other antibiotics. The maximum daily dose for adults is 4.0 g independent of the dose of the combined antibiotic. A dosage of 6 grams per day in divided doses of sulbactam alone may be considered in multidrug resistant, life threatening *Acinetobacter baumanni* infections, if renal function is normal. Sulbactam (0.5 to 1 gm) should be administered in combination with an antibiotic at the time of infection for the preoperative short term prophylaxis where the patient has a high infection risk. Period of administration depends on the course of disease and should be continued per clinical indications.

Pediatric Dosage

Pediatric patients who weigh 40 kg or more may receive the usual adult dosage of sulbactam sodium.

Renal Impairment

In patients with impaired renal function, the dose and/or frequency of administration of sulbactam sodium should be modified in response to the degree of renal impairment, severity of infection, and susceptibility of the causative organisms.

Directions for Use

For 1gm dissolve the contents 3.2mL of Sterile Water for Injections IP for IM use and for IV use, first dissolve in 7mL of Sterile Water for Injections IP and further dilute it if required . For 2gm dissolve the contents in 6.4mL of Sterile Water for Injections IP for IM use and for IV use, first dissolve in 14mL of Sterile Water for Injections IP and further dilute it if required. The reconstituted solution should be used immediately after preparation. Do not use in case any foreign particulate is observed inside the vial.

Contraindications

Sulbactam injection should not be used in known hypersensitivity situations against beta-lactam antibiotic combinations.

Special Warnings and Precautions for Use

As sulbactam is available as a sodium salt solution, care should be exercised

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regarding the amounts of sodium in patients with electrolyte disorder. As identified with other beta-lactams, it could result in central nervous system excitation, myocontractions, and cramps. The risk is increased in patients with significant renal function impairment, epilepsy, and meningitis. Pregnancy is considered as risk-category B.

Pediatric Precautions
Safety and efficacy of IV beta lactam antibiotic combinations in children 1 year of age or older have been established for the treatment of skin and skin structure infections. Various fixed dose combinations of sulbactam (eg, 1.3:1, 2:1, 3:1, 4:1, 7:1, and 8:1 ratios of ampicillin to sulbactam) have been administered IM or IV to neonates and children 1 month to 17 years of age without unusual adverse effects. The most frequent adverse effects observed are transient increases in serum liver enzyme concentrations, diarrhea, and rash.

Geriatric Population
Sulbactam sodium does not need to be modified in geriatric patients with normal renal function.

Drug Interactions
Aminoglycosides
Sulbactam is incompatible with aminoglycosides and can in *vitro* inactivate the drugs. In one in *vitro* study, sulbactam concentrations of 25 mcg/mL had no appreciable effect on aminoglycosides in serum at 37°C. However, at concentrations of 75 mcg/mL, sulbactam inactivated tobramycin (but not the other aminoglycosides tested) and, at concentrations of 200 mcg/mL or greater (with or without ampicillin), sulbactam inactivated amikacin, gentamicin, netilmicin and tobramycin. Some clinicians suggest that in *vivo* inactivation of aminoglycosides by sulbactam is unlikely to occur, as sulbactam concentrations of 25 mcg/mL usually are not achieved clinically.

Probenecid
Delayed sulbactam excretion is seen when co-administered with probenecid. There is no information on occurrence of an interaction because of sulbactam addition, which is not observed in beta-lactam antibiotic combinations without sulbactam addition, in trials performed for sulbactam in combination with beta-lactam antibiotics. All interactions reported for sulbactam in combination with mezlocillin, piperacillin, cefotaxime, or penicillin G are possible interactions due to the antibiotic component.

Pregnancy and Lactation
Pregnancy Category B
There are no adequate or controlled studies in pregnant women, and the drug should be used during pregnancy only when clearly indicated.

Lactation
Although sulbactam is distributed into breast milk in small amounts, no adverse effects have been seen in breast-fed infants and the American Academy of Pediatrics considers that it is usually compatible with breast feeding.

Effects on Ability to Drive and Use Machines
None reported.

Undesirable Effects
The most frequent adverse effects of beta-lactam antibiotic combinations (parenteral ampicillin sodium and sulbactam sodium) are pain at the injection site. Parenteral sulbactam sodium alone is associated with few adverse effects, principally pain at the injection site and diarrhea.

All side effects reported for sulbactam in combination with mezlocillin, cefotaxime, or penicillin G are possible side effects of the antibiotic component. Very rare side effects were observed with beta-lactam antibiotics that can be combined with sulbactam (thrombocytopenia, leucopenia, lecocytosis, neutropenia, anemia, and eosinophilia). In high-doses mexlocillin or piperacillin treatment, rare cases of bleeding time prolongation, thrombocyte function disturbances exhibited as small-spotted bleeding on skin or mucous membrane (purpura), uncommon allergic reactions, dizziness, headache, dyspepsia, nausea, vomiting, loss of appetite, accumulation of gas, and diarrhea may be observed.

Overdose
The molecular weight, degree of protein binding, and pharmacokinetics profile of sulbactam suggest that this compound may be removed by hemodialysis. This procedure may enhance elimination of the drug from the body if overdose occurs in patients with impaired renal function; this procedure is probably unnecessary in patients with normal renal function.

PHARMACEUTICAL PARTICULARS
Incompatibilities
None reported.

Special Precautions for Disposal and Other Handling
None.

Nature and Contents of Container
MATABAC™ (Sulbactam Sodium for Injection, 1 g)
10mL moulded glass clear vial with 10 mL Water for Injections IP

MATABAC™ 2g (Sulbactam Sodium for Injection, 2 g)
20 mL moulded glass vial with 20mL Sterile Water For Injections IP

Storage: store in a dry & dark place, below 25°C. Do not freeze.
Keep out of reach of children.

MANUFACTURED BY
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