SULBACIP I.V. Injection (Sulbactam sodium)

Composition

SULBACIP I.V. 1 gm
Each vial contains:
Sulbactam Sodium USP equivalent to Sulbactam...... 1 gm

SULBACIP I.V. 2 gm
Each vial contains:
Sulbactam Sodium USP equivalent to Sulbactam ...... 2 gm

Dosage Form

Powder for reconstitution (intravenous )

Pharmacology

Sulbactam is a derivative of the basic penicillin nucleus. Chemically, sulbactam sodium is sodium penicillinate sulphone; sodium (2S, 5R)-3, 3-dimethyl-7-oxo-4-thia-1-azabicyclo heptanes-2-carboxylate 4, 4-dioxide. Its chemical formula is $C_{8}H_{11}NaO_{5}S$, with a molecular weight of 255.22. It contains 92 mg sodium (4 mEq) per gram. Its structural formula is

\[
\text{COONa} \quad \text{CH}_3 \quad \text{CH}_3
\]

\[
\text{O} \quad \text{N} \quad \text{S}
\]

Pharmacodynamics

Sulbactam is a synthetic beta-lactamase inhibitor. A feature that distinguishes sulbactam from other available beta-lactamase inhibitors is its direct antimicrobial activity against the Acinetobacter species and Bacteroides fragilis. Its mechanism of antimicrobial activity against Acinetobacter baumannii (A. baumannii) strains is related to its intrinsic affinity for the essential penicillin-binding proteins (PBPs) of these organisms, and for altering the permeability of the outer membrane of Gram-negative bacilli, resulting in the leakage of beta-lactamases and, thus, better penetration by other antibacterial agents.

It is not clear whether combination therapy with sulbactam improves efficacy over monotherapy for highly drug-resistant
A. baumannii. Many of the data come from in vitro and animal models, which show enhanced activity when sulbactam is combined with cefepime, imipenem, meropenem, colistin, amikacin, rifampicin and ticarcillin-clavulanate. Such enhanced activity may also be retained for infections with sulbactam non-susceptible organisms.

## Pharmacokinetics

### Absorption

After a 30-minute infusion of 1g of sulbactam, a peak concentration of approximately 43 mcg/mL is obtained.

![Concentration-time profile of sulbactam](image)

Multiple dosing at rates as high as 500 mg every 6 hours (intramuscular) or 1 g twice a day (1-hour infusions or I.V. bolus) does not appear to lead to accumulation of the drug as indicated by an increase in the peak serum concentrations or the AUCs.

### Distribution

The binding of sulbactam to human serum proteins is approximately 38%. In a two-compartment pharmacokinetic model, the apparent volume of distribution of the central compartment of 9 to 16 litres is in the range of total extracellular fluid in humans (approximately 15 litres) and suggests that sulbactam is widely distributed in the extracellular fluid.

The total apparent volume of distribution of between 19 and 28 litres is over half that of the total body fluid, approximately 40 litres in a 70 kg human, suggesting that sulbactam may be widely distributed into the tissues. An hour after I.V. administration of 1 g sulbactam (at its peak concentration in serum) in 8 patients with bacterial respiratory infections, a penetration ratio (alveolar lavage fluid versus serum) of 61% has been reported. In patients with inflamed meninges; the cerebrospinal fluid (CSF) penetration of sulbactam is reported to be 2-32% of serum levels, which are approximately 42-60 mg/L after a 1 g I.V. dose. After 500 mg of a parenteral dose, appreciable concentrations were observed in peritoneal fluid (14 mg/L), intestinal mucosa (0-28 mg/g), prostate (7mg/g) and pus (12.7 mg/L).

### Metabolism and Excretion

The mean serum half-life is approximately 1 hour in healthy volunteers. Approximately 70% of a parenteral dose of sulbactam was excreted in the urine between 0 and 6 hours, with an additional recovery of 5% between 6 and 12 hours post-dose. The renal clearance is approximately 204 ml/min and was not dose-dependent. The total clearance of drug from the serum was 266 mL/min. The non-renal clearance was 65 mL/min.

An additional similarity to the beta-lactam antibiotics is the increase in the half-life of sulbactam of approximately 40% in humans due to a prior dose of probenecid.

### Use in Renal Impairment

In patients with different degrees of renal function who were administered sulbactam/cefoperazone, the total body
clearance of sulbactam was highly correlated with the estimated creatinine clearance. Patients who were functionally anephric showed a significantly longer half-life of sulbactam (mean 6.9 and 9.7 hours in separate studies). Haemodialysis removes 30% of the given doses of sulbactam and, hence, supplemental doses are recommended after dialysis.

Use in Hepatic Impairment

Sulbactam in combination with ampicillin has been administered safely in I.V. doses of 3-9 g/day in patients with chronic liver disease. Adverse effects observed were minor (oral candidiasis and local injection-site pain) and infrequent; blood chemistry tests were unchanged following therapy.

Use in Paediatric Patients (2 to 14 years of age)

Single doses of 12.5 or 25 mg/kg infused over 3 minutes results in mean peak plasma concentrations of 71 or 163 mcg/ml after 5 minutes of dosing. The mean terminal-phase half-life was 1.75 hours, the mean total plasma clearance was 180 ml/min/1.73 m2, and the mean apparent volume of distribution was 340 ml/kg. Approximately 70-80% of an I.V. dose was excreted unchanged in the urine. In children with cystic fibrosis, both the total plasma clearance and the apparent volume of distribution were significantly increased.

Use in Geriatric Patients

Comparative pharmacokinetic data for sulbactam in young and elderly individuals suggest that there is a prolongation of antimicrobial activity as age increases, which is due to the area under the serum concentration-time curve, half-life, serum maximum concentration and decreased total clearance in the older age group.

Indications

SULBACIP I.V. is indicated in the treatment of the following infections, where sensitivity testing suggests that they are caused by susceptible bacteria:

Treatment of some serious infections caused by multidrug-resistant (MDR) Acinetobacter and ESBLs infections, including those of the lower respiratory tract, bacteraemia/sepsis, meningitis, surgical wounds, and the urinary tract, when more commonly used systemic antibacterial agents may be contraindicated or may be ineffective because of bacterial resistance.

Dosage And Administration

Dosage

Adults with Normal Renal Function

1. For ESBLs infections when used in combination with beta-lactam antibiotic, dosing up to 4g/day of SULBACIP I.V
2. For serious Acinetobacter infections, dosing up to minimum of 6g/day of SULBACIP I.V. in three equal divided doses, in combination with antibacterials active against Acinetobacter is recommended

Renal Impairment

Dosage regimens of sulbactam should be adjusted in patients with marked decrease in renal function (creatinine clearance of less than 30 mL/min) to compensate for the reduced renal clearance of sulbactam.

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Maximum Dosage</th>
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<tr>
<td>15-30</td>
<td>1 g b.i.d</td>
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The pharmacokinetic profile of sulbactam is significantly altered by haemodialysis. The dosing should be scheduled to follow a dialysis period.

Paediatric Use
The recommended dose of sulbactam when administered along with cefoperazone and ampicillin is 80-100 mg/kg/day in two to four equally divided doses.

Method of Preparation
- **SULBACIP I.V. 1 gm**
  Reconstitute with 6.2 mL of 5% Dextrose, 0.9% Sodium Chloride Injection or Sterile Water for Injection, then further dilute to 20 mL of the same solution.
- **SULBACIP I.V. 2 gm**
  Reconstitute with 12.4 mL of 5% Dextrose, 0.9% Sodium Chloride Injection or Sterile Water for Injection, then further dilute to 40 mL of the same solution.

Method of Administration
SULBACIP I.V. should be administered over a period of 15 to 60 minutes.

Contraindications
Sulbactam is contraindicated in patients with a known allergy/hypersensitivity to beta-lactam antibiotics.

Warnings And Precautions

- **General**
  Before therapy with SULBACIP I.V. is initiated, careful inquiry should be made concerning previous hypersensitivity reactions and other allergens. Hypersensitivity reactions, including skin rash, urticaria, pruritus, fever and anaphylaxis, have been observed. If allergic reactions occur, SULBACIP I.V. should be discontinued and the appropriate therapy be instituted.
  In case serious anaphylactic reactions occur with SULBACIP I.V. use, it requires immediate emergency treatment with epinephrine. Oxygen, I.V. steroids and airway management, including intubation, should be administered as indicated.
  Treatment with antibacterial agents alters the normal flora of the colon, leading to the overgrowth of *Clostridium difficile* (*C. difficile*). If *C. difficile*-associated diarrhoea (CDAD) is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.
  As with any potent systemic agent, it is advisable to check periodically for organ system dysfunction during extended therapy; this includes the renal, hepatic and haematopoietic systems. This is particularly important in neonates, especially when premature, and other infants.

- **Drug Interactions**
  Probenecid decreases the renal tubular secretion of sulbactam. Concurrent use of probenecid may result in increased and prolonged blood levels of sulbactam.
Renal Impairment

Please refer under 'PHARMACOLOGY' and 'DOSAGE AND ADMINISTRATION'.

Hepatic Impairment

No data is available on sulbactam alone; however, when used with ampicillin at I.V. doses of 3-9 g/day in patients with chronic liver disease, adverse effects observed were minor (oral candidiasis and local injection-site pain) and infrequent; blood chemistry tests were unchanged following therapy.

Pregnancy

Reproduction studies of sulbactam in combination with ampicillin and cefoperazone have been performed in rats at doses up to 10 times the human dose and have revealed no evidence of impaired fertility and no teratogenic findings. Sulbactam is known to cross the placental barrier. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, sulbactam should be used during pregnancy only if clearly needed.

Lactation

Although only small quantities of sulbactam are excreted in human milk, caution should be exercised when sulbactam is administered to a nursing mother.

Paediatric Use

Please refer under PHARMACOLOGY and DOSAGE AND ADMINISTRATION.

Geriatric Use

Please refer under PHARMACOLOGY and DOSAGE AND ADMINISTRATION.

Undesirable Effects

There is limited data on undesirable effects with sulbactam alone. However, sulbactam in combination with ampicillin and cefoperazone has been generally well-tolerated. As with other antibiotics, the most frequent side effects observed with sulbactam when used in combination have been gastrointestinal like diarrhoea/loose stools (3.09%), and nausea and vomiting (0.6%). Additional systemic reactions reported in less than 1% of the patients were itching, candidiasis, fatigue, malaise, headache, chest pain, flatulence, abdominal distension, glossitis, urine retention, dysuria, oedema, facial swelling, erythema, chills, tightness in the throat, substernal pain, epistaxis and mucosal bleeding. Laboratory changes most commonly reported involved elevated hepatic enzymes (AST, ALT, alkaline phosphatase, lactate dehydrogenase). Haematological abnormalities (decreased haematocrit/haemoglobin, leucopenia, lymphopenia, thrombocytopenia or increased lymphocytes, monocytes, basophils, eosinophils and platelets), decreased albumin and total proteins, increased creatinine, and the presence of red blood cells and hyaline casts in urine are less frequent.

Overdosage

Limited information is available on the acute toxicity of sulbactam sodium in humans. The molecular weight, degree of protein binding and pharmacokinetics profile of sulbactam suggest that this compound may be removed by haemodialysis.

Incompatibility
When concomitant therapy with other antibacterials is indicated, SULBACIP I.V. should be reconstituted and administered separately.

Storage And Handling Instructions

Before Opening
Store below 25°C. Protect from light.

Reconstituted Solution
Reconstituted solution is stable for 7 days at 2-8°C and for 24 hours at room temperature.

Packaging Information

SULBACIP I.V. 1 gm: Available in a vial of 20 mL
SULBACIP I.V. 2 gm: Available in a vial of 20 mL

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