PFIZER

UNASYN IM/IV*
Sulbactam Sodium / Ampicillin Sodium

DESCRIPTION

Sulbactam sodium is a derivative of the basic penicillin nucleus. Chemically it is sodium penicillanate sulfone and is an off-white crystalline powder highly soluble in water. The molecular weight is 255.22.

Ampicillin sodium is derived from the penicillin nucleus, 6-aminopenicillanic acid. Chemically, it is D(-)-α-aminobenzyl penicillin sodium salt and has a molecular weight of 371.39.

UNASYN IM/IV, brand of sulbactam sodium/ampicillin sodium combination, is available as a dry powder for reconstitution in vials containing the equivalent of 250 mg + 500 mg of sulbactam and ampicillin.

ACTIONS

Biochemical studies with cell-free bacterial systems have shown sulbactam to be an irreversible inhibitor of most important beta-lactamases that occur in penicillin-resistant organisms. While sulbactam's antibacterial activity is mainly limited to *Neisseriaceae*, the potential for sulbactam sodium in preventing the destruction of penicillins and cephalosporins by resistant organisms was confirmed in whole organism studies using resistant strains, in which sulbactam sodium exhibited marked synergistic effects with penicillins and cephalosporins. Since sulbactam also binds to some penicillin-binding proteins, some sensitive strains are rendered more susceptible to the combination than to the beta-lactam antibiotic alone.

The bactericidal component of the combination is ampicillin which, like benzyl penicillin, acts against sensitive organisms during the stage of active multiplication by the inhibition of biosynthesis of cell wall mucopeptide.

UNASYN IM/IV is effective against a wide range of Gram-positive and Gram-negative bacteria including:
Staphylococcus aureus and *epidermidis* (including penicillin-resistant and some methicillin-resistant strains); *Streptococcus pneumoniae*, *Streptococcus faecalis* and other *Streptococcus* species; *Haemophilus influenzae* and *parainfluenzae* (both beta-lactamase positive and negative strains); *Branhamella catarrhalis*; anaerobes, including *Bacteroides fragilis* and related species; *Escherichia coli*, *Klebsiella* species, *Proteus* species (both indole-positive and indole-negative), *Morganelli morganii*, *Citrobacter* species, *Enterobacter* species, *Neisseria meningitidis* and *Neisseria gonorrhoeae*.

Sulbactam/ampicillin diffuses readily into most body tissues and fluids in the human. Penetration into brain and spinal fluid is low except when meninges are inflamed.

High concentrations of sulbactam and ampicillin are achieved in the blood following intravenous or intramuscular administration and both components have a half life of approximately 1 hour. Most of the sulbactam/ampicillin is excreted unchanged in the urine.

INDICATIONS

UNASYN IM/IV is indicated for infections caused by susceptible microorganisms. Typical indications are upper and lower respiratory tract infections including sinusitis, otitis media and epiglottitis; bacterial pneumonias; urinary tract infections and pyelonephritis; intra-abdominal infections including peritonitis, cholecystitis, endometritis and pelvic cellulitis; bacterial septicemia; skin, soft tissue, bone and joint infections and gonococcal infections.

UNASYN IM/IV may also be administered peri-operatively to reduce the incidence of post-operative wound infections in patients undergoing abdominal or pelvic surgery, in which peritoneal contamination may be present. In termination of pregnancy or cesarean section, UNASYN IM/IV may be used prophylactically to reduce post-operative sepsis.

CONTRAINDICATIONS

The use of this combination is contraindicated in individuals with a history of an allergic reaction to any of the penicillins.

WARNINGS

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more apt to occur in individuals with a history of penicillin hypersensitivity and/or hypersensitivity reactions to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the appropriate therapy instituted.

Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should be administered as indicated.

Use In Pregnancy and Lactation

Animal reproduction studies have revealed no evidence of impaired fertility or harm to the fetus due to sulbactam and ampicillin. Sulbactam crosses the placental barrier. Safety for use in pregnancy and lactation has not been established.

PRECAUTIONS

As with any antibiotic preparation, constant observation for signs of overgrowth of nonsusceptible organisms, including fungi, is essential. Should superinfection occur, the drug should be discontinued and/or appropriate therapy instituted.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including sulbactam sodium/ampicillin sodium, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C difficile.*

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

As with any potent systemic agent, it is advisable to check periodically for organ system dysfunction during extended therapy; this includes renal, hepatic, and hematopoietic systems. This is particularly important in neonates, especially when premature, and other infants.

Since infectious mononucleosis is viral in origin, sulbactam sodium/ampicillin sodium IM/IV should not be used in its treatment. A high percentage of patients with mononucleosis who received ampicillin have developed a skin rash.

INTERACTION WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION

Allopurinol: The concurrent administration of allopurinol and ampicillin substantially increases the incidence of rashes in patients receiving both drugs as compared with patients receiving ampicillin alone.

Aminoglycosides: Mixing ampicillin with aminoglycosides in vitro has resulted in substantial mutual inactivation; if these groups of antibacterials are to be administered concurrently, they should be administered at separate sites at least 1 hour apart.

Anticoagulants: Parenteral penicillins can produce alterations in platelet aggregation and coagulation tests. These effects may be additive with anticoagulants.

Bacteriostatic drugs (chloramphenicol, erythromycin, sulfonamides and tetracyclines): Bacteriostatic drugs may interfere with the bactericidal effect of penicillins; it is best to avoid concurrent therapy.

Estrogen-containing oral contraceptives: There have been case reports of reduced oral contraceptive effectiveness in women taking ampicillin, resulting in unplanned pregnancy. Although the association is weak, patients should be given the option to use an alternate or additional method of contraception while taking ampicillin.

Methotrexate: Concurrent use with penicillins has resulted in decreased clearance of methotrexate and in methotrexate toxicity. Patients should be closely monitored. Leucovorin dosages may need to be increased and administered for longer periods of time.

Probenecid: Probenecid decreases renal tubular secretion of ampicillin and sulbactam when used concurrently; this effect results in increased and prolonged serum concentrations, prolonged elimination half-life, and increased risk of toxicity.

ADVERSE REACTIONS

As with other parenteral antibiotics, the principal side effect observed is injection site pain, especially associated with the intramuscular route of administration. A small number of patients may develop phlebitis after intravenous administration.

Blood and Lymphatic System Disorders: anemia, hemolytic anemia, thrombocytopenia, eosinophilia and leukopenia have been reported during therapy with sulbactam sodium/ampicillin sodium. These reactions are reversible on discontinuation of therapy and are believed to be sensitivity reactions.

Gastrointestinal Disorders: nausea, vomiting, diarrhea, enterocolitis and pseudomembranous colitis

Hepatobiliary Disorders: bilirubinemia, abnormal hepatic function and jaundice

Immune System Disorders: anaphylactoid reaction and anaphylactic shock

Investigations: transient elevations of ALT (SGPT) and AST (SGOT) transaminases

Nervous System Disorders: rare reports of convulsions

Renal and Urinary Disorders: rare reports of interstitial nephritis

Skin and Subcutaneous Tissue Disorders: rash, itching, other skin reactions, rare reports of Stevens-Johnson syndrome, epidermal necrolysis and erythema multiforme

Adverse reactions associated with the use of ampicillin alone may be observed with sulbactam sodium/ampicillin sodium IM/IV.

DOSAGE AND ADMINISTRATION

UNASYN IM/IV can be administered by either intravenous or intramuscular routes. The following dilutions may be used:

Total Dosage	Equivalent Dosage of Sulbactam-	Package	Diluent Volume	Maximum Final Concentration

(g)	Ampicillin (g)		(ml)	(mg/ml)
0.75	0.25 - 0.5	10 ml vial	1.6	125 - 250

For intravenous administration, UNASYN IM/IV should be reconstituted with sterile water for injection or any compatible solution. To ensure complete dissolution, allow foaming to dissipate in order to visually inspect. The dose can be given by bolus injection over a minimum of 3 minutes or can be used in greater dilutions as an intravenous infusion over 15-30 minutes.

Pfizer sulbactam sodium/ampicillin sodium parenteral may also be administered by deep intramuscular injection; if pain is experienced, 0.5% sterile solution for injection of lignocaine hydrochloride anhydrous may be used for reconstitution of the powder.

The usual dosage range of UNASYN IM/IV is 1.5 g to 12 g per day in divided doses every 6 or 8 hours up to a maximum daily dosage of sulbactam of 4 g. Less severe infections may be treated on an every-12-hours schedule.

SEVERITY OF INFECTION	DAILY DOSE OF UNASYN IM/IV (g)
Mild	1.5 to 3 (0.5 + 1 to 1 + 2)
Moderate	up to 6 (2 + 4)
Severe	up to 12 (4 + 8)

The dosage of UNASYN IM/IV for most infections in children, infants and neonates is 150 mg/kg/day (corresponding to sulbactam 50 mg/kg/day and ampicillin 100 mg/kg/day). In children, infants and neonates dosing is usually every 6 or 8 hours in accordance with the usual practice for ampicillin. In neonates during the first week of life (especially preterms), dosing is usually every 12 hours.

More or less frequent dosing may be indicated depending on the severity of the illness and the renal function of the patient.

Treatment is usually continued until 48 hours after pyrexia and other abnormal signs have resolved. Treatment is normally given for 5 to 14 days, but the treatment period may be extended or additional ampicillin may be administered in severely ill cases.

In patients with severe impairment of renal function (creatinine clearance 30 ml/min), the elimination kinetics of sulbactam and ampicillin are similarly affected and hence the plasma ratio of one to the other will remain constant. The dose of UNASYN IM/IV in such patients should be administered less frequently in accordance with the usual practice for ampicillin.

In treating patients on restricted sodium intake, it should be noted that 1,500 mg of UNASYN IM/IV contains approximately 115 mg (5 mmol) of sodium.

For the prophylaxis of surgical infections, 1.5-3 g of UNASYN IM/IV should be given at induction of anesthesia, which allows sufficient time to achieve effective serum and tissue concentrations during the procedure. The dose may be repeated

every 6-8 hours; administration is usually stopped 24 hours after the majority of surgical procedures, unless a therapeutic course of UNASYN IM/IV is indicated.

In the treatment of uncomplicated gonorrhea, UNASYN IM/IV can be given as a single dose of 1.5 g. Concomitant probenecid 1.0 g orally should be administered in order to prolong plasma concentrations of sulbactam and ampicillin.

Stability and Compatibility

Sulbactam sodium is compatible with most intravenous solutions but ampicillin sodium and hence UNASYN IM/IV is less stable in solutions containing dextrose or other carbohydrates, and should not be mixed with blood products or protein hydrolysates. Ampicillin and hence UNASYN IM/IV is incompatible with aminoglycosides and should not be physically mixed in the same container.

Intravenous use:

Time periods for use in different diluents for intravenous infusion are as follows:

Diluent	Concentration Sulbactam + ampicillin	Use Periods (In Hours)	
		25°C	4°C
Sterile Water For Injection	up to 45 mg/ml	8	48
	up to 30 mg/ml		72
Isotonic Sodium Chloride	up to 45 mg/ml	8	48
	up to 30 mg/ml		72
M/6 Sodium Lactate Solution	up to 45 mg/ml	8	8
5% Dextrose in Water	15 to 30 mg/ml	2	
	up to 3 mg/ml	4	
	up to 30 mg/ml		4
5% Dextrose in 0.45% NaCl	up to 3 mg/ml	4	
	up to 15 mg/ml		4
10% Invert Sugar in Water	up to 3 mg/ml	4	
	up to 30 mg/ml		3
Lactated Ringer's Solution	up to 45 mg/ml	8	24

Intramuscular use:

Vials for intramuscular use may be reconstituted with Sterile Water for Injection USP, 0.5% Lidocaine Hydrochloride Injection USP or 2% Lidocaine Hydrochloride Injection USP. Consult the following table for recommended volumes to be added to obtain solutions containing 375 mg UNASYN per ml (250 mg ampicillin/125 mg sulbactam per ml). The concentrated solution for intramuscular administration should be used within 1 hour of reconstitution.

UNASYN Vial Size	Volume of Diluent to be added	Withdrawal volume*
0.75 g	1.6 ml	2.0 ml

*There is sufficient excess present to allow withdrawal and administration of the stated volumes.

Shelf Life
Refer to carton for shelf-life.

Nature and Contents of Container
Neutral glass vials containing 250 mg sulbactam and 500 mg ampicillin powder for reconstitution.

Instruction for Use/Handling
To be dispensed only by or on the prescription of a physician.
Keep out of the reach of children.

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