

## Ampicillin and Sulbactam for Injection, USP

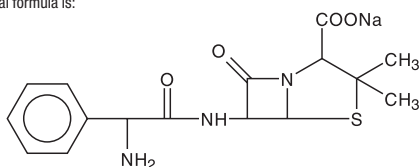
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Ampicillin and Sulbactam for Injection and other antibacterial drugs, Ampicillin and Sulbactam for Injection should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

### DESCRIPTION

Ampicillin and Sulbactam for Injection, USP is an injectable antibacterial combination consisting of the semisynthetic antibacterial ampicillin sodium and the beta-lactamase inhibitor sulbactam sodium for intravenous and intramuscular administration.

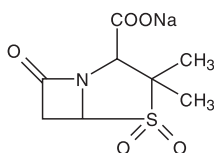
Ampicillin sodium is derived from the penicillin nucleus, 6-aminopenicillanic acid. Chemically, it is monosodium (2S, 5R, 6R)-6-[(R)-2-amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate and has a molecular weight of 371.39. Its chemical formula is  $C_{16}H_{18}N_3NaO_4S$ .

The structural formula is:



Sulbactam sodium is a derivative of the basic penicillin nucleus. Chemically, sulbactam sodium is sodium penicillinate sulfone; sodium (2S, 5R)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide. Its chemical formula is  $C_9H_{10}NNaO_5S_2$  with a molecular weight of 255.22.

The structural formula is:



Ampicillin and Sulbactam for Injection, USP parenteral combination, is available as a white to yellowish dry powder for reconstitution. Ampicillin and Sulbactam for Injection, USP dry powder is freely soluble in aqueous diluents to yield pale yellow to yellow solutions containing ampicillin sodium and sulbactam sodium equivalent to 250 mg ampicillin per mL and 125 mg sulbactam per mL. The pH of the solutions is between 8 and 10.

Dilute solutions (up to 30 mg ampicillin and 15 mg sulbactam per mL) are essentially colorless to pale yellow. The pH of dilute solutions remains the same.

Each 1.5 gram vial contains 1.5 g Ampicillin and Sulbactam for Injection, USP (equivalent to 1 g ampicillin as the sodium salt plus 0.5 g sulbactam as the sodium salt). The sodium content is 115 mg (5 mEq).

Each 3 gram vial contains 3 g Ampicillin and Sulbactam for Injection, USP (equivalent to 2 g ampicillin as the sodium salt plus 1 g sulbactam as the sodium salt). The sodium content is 230 mg (10 mEq).

### CLINICAL PHARMACOLOGY

#### General

Immediately after completion of a 15-minute intravenous infusion of Ampicillin and Sulbactam, peak serum concentrations of ampicillin and sulbactam are attained. Ampicillin serum levels are similar to those produced by the administration of equivalent amounts of ampicillin alone. Peak ampicillin serum levels ranging from 109 to 150 mcg/mL are attained after administration of 2000 mg of ampicillin plus 1000 mg sulbactam and 40 to 71 mcg/mL after administration of 1000 mg ampicillin plus 500 mg sulbactam. The corresponding mean peak serum levels for sulbactam range from 48 to 88 mcg/mL and 21 to 40 mcg/mL, respectively. After an intramuscular injection of 1000 mg ampicillin plus 500 mg sulbactam, peak ampicillin serum levels ranging from 8 to 37 mcg/mL and peak sulbactam serum levels ranging from 6 to 24 mcg/mL are attained.

The mean serum half-life of both drugs is approximately 1 hour in healthy volunteers.

Approximately 75 to 85% of both ampicillin and sulbactam are excreted unchanged in the urine during the first 8 hours after administration of Ampicillin and Sulbactam to individuals with normal renal function. Somewhat higher and more prolonged serum levels of ampicillin and sulbactam can be achieved with the concurrent administration of probenecid.

In patients with impaired renal function the elimination kinetics of ampicillin and sulbactam are similarly affected, hence the ratio of one to the other will remain constant whatever the renal function. The dose of Ampicillin and Sulbactam for Injection in such patients should be administered less frequently in accordance with the usual practice for ampicillin (see *Dosage and Administration*).

Ampicillin has been found to be approximately 28% reversibly bound to human serum protein and sulbactam approximately 38% reversibly bound.

The following average levels of ampicillin and sulbactam were measured in the tissues and fluids listed:

TABLE 1. Concentration of Ampicillin and Sulbactam for Injection in Various Body Tissues and Fluids

Fluid or Tissue	Dose (grams) Ampicillin/Sulbactam	Concentration (mcg/mL or mcg/g) Ampicillin/Sulbactam
Peritoneal Fluid	0.5/0.5 IV	7/14
Blister Fluid (Cantharides)	0.5/0.5 IV	8/20
Tissue Fluid	1/0.5 IV	8/4
Intestinal Mucosa	0.5/0.5 IV	11/18
Appendix	2/1 IV	3/40

Penetration of both ampicillin and sulbactam into cerebrospinal fluid in the presence of inflamed meninges has been demonstrated after IV administration of Ampicillin and Sulbactam.

The pharmacokinetics of ampicillin and sulbactam in pediatric patients receiving Ampicillin and Sulbactam are similar to those observed in adults. Immediately after a 15-minute infusion of 50 to 75 mg Ampicillin and Sulbactam/kg body weight, peak serum and plasma concentrations of 82 to 446 mcg ampicillin/mL and 44 to 203 mcg sulbactam/mL were obtained. Mean half-life values were approximately 1 hour.

### MICROBIOLOGY

Ampicillin is similar to benzyl penicillin in its bactericidal action against susceptible organisms during the stage of active multiplication. It acts through the inhibition of cell wall mucopeptide biosynthesis. Ampicillin has a broad spectrum of bactericidal activity against many gram-positive and gram-negative aerobic and anaerobic bacteria. (Ampicillin is, however, degraded by beta-lactamases and therefore the spectrum of activity does not normally include organisms which produce these enzymes).

A wide range of beta-lactamases found in microorganisms resistant to penicillins and cephalosporins have been shown in biochemical studies with cell free bacterial systems to be irreversibly inhibited by sulbactam. Although sulbactam alone possesses little useful antibacterial activity except against the *Neisseriaceae*, whole organism studies have shown that sulbactam restores ampicillin activity against beta-lactamase producing strains. In particular, sulbactam has good inhibitory activity against the clinically important plasmid mediated beta-lactamases most frequently responsible for transferred drug resistance. Sulbactam has no effect on the activity of ampicillin against ampicillin susceptible strains.

The presence of sulbactam in the Ampicillin and Sulbactam for Injection formulation effectively extends the antibacterial spectrum of ampicillin to include many bacteria normally resistant to it and to other beta-lactam antibiotics. Thus, Ampicillin and Sulbactam possesses the properties of a broad-spectrum antibacterial and a beta-lactamase inhibitor.

While *in vitro* studies have demonstrated the susceptibility of most strains of the following organisms, clinical efficacy for infections other than those included in the **INDICATIONS AND USAGE** section has not been documented.

**Gram-Positive Bacteria:** *Staphylococcus aureus* (beta-lactamase and non-beta-lactamase producing), *Staphylococcus epidermidis* (beta-lactamase and non-beta-lactamase producing), *Staphylococcus saprophyticus* (beta-lactamase and non-beta-lactamase producing), *Streptococcus faecalis* (Enterococcus), *Streptococcus pneumoniae* (formerly *D. pneumoniae*), *Streptococcus pyogenes*, *Streptococcus viridans*.

**Gram-Negative Bacteria:** *Hemophilus influenzae* (beta-lactamase and non-beta-lactamase producing), *Moraxella (Branhamella) catarrhalis* (beta-lactamase and non-beta-lactamase producing), *Escherichia coli* (beta-lactamase and non-beta-lactamase producing), *Klebsiella* species (all known strains are beta-lactamase producing), *Proteus mirabilis* (beta-lactamase and non-beta-lactamase producing), *Proteus vulgaris*, *Providencia rettgeri*, *Providencia stuartii*, *Morganella morganii*, and *Neisseria gonorrhoeae* (beta-lactamase and non-beta-lactamase producing).

**Anaerobes:** *Clostridium* species†, *Peptococcus* species†, *Peptostreptococcus* species, *Bacteroides* species, including *B. fragilis*.

†These are not beta-lactamase producing strains and, therefore, are susceptible to ampicillin alone.

### Susceptibility Testing

#### Diffusion Technique

For the disk diffusion method of susceptibility testing, a 20 mcg (10 mcg ampicillin + 10 mcg sulbactam) disk should be used. The standardized procedure<sup>1,2</sup> requires the use of a standardized inoculum concentration. With this procedure, a report from the laboratory of "Susceptible" indicates that the infecting organism is likely to respond to Ampicillin and Sulbactam therapy and a report of "Resistant" indicates that the infecting organism is not likely to respond to therapy.

An "Intermediate" susceptibility report suggests that the infecting organism would be susceptible to Ampicillin and Sulbactam if a higher dosage is used or if the infection is confined to tissues or fluids (e.g., urine) in which high antibacterial levels are attained.

#### Dilution Techniques

Broth, agar, microdilution or equivalent methods may be used to determine the minimal inhibitory concentration (MIC) value for susceptibility of bacterial isolates using standardized methods, inoculums and concentrations of ampicillin/sulbactam.<sup>2,3,4</sup>

The recommended dilution method employs a constant ampicillin/sulbactam ratio of 2:1 in all tubes with increasing concentrations of ampicillin. MIC's are reported in terms of ampicillin concentration in the presence of sulbactam at a constant 2 parts ampicillin to 1 part sulbactam.

TABLE 2. Recommended Ampicillin/Sulbactam, Disk Diffusion and MIC Susceptibility Ranges\*†‡ (Zone diameter in mm)

Organisms	Inhibition zone diameter (mm)			MIC (mcg/mL of ampicillin)		
	Resistant	Intermediate	Susceptible	Resistant	Intermediate	Susceptible
<i>Enterobacteriaceae</i> , <i>Acinetobacter calcoaceticus</i> , <i>Staphylococcus</i> spp.	≤11	12–14	≥15	≥32	16	≤8
<i>Haemophilus influenzae</i>	≤19	--	≥20	≥4	--	≤2

\* The non-beta-lactamase producing organisms which are normally susceptible to ampicillin, such as *Streptococci*, will have similar zone sizes as for ampicillin disks.

† *Staphylococci* resistant to methicillin, oxacillin, or nafcillin must be considered resistant to ampicillin/sulbactam.

‡ The quality control cultures should have the following assigned daily ranges for ampicillin/sulbactam (see TABLE 3):

TABLE 3. Quality Control Ranges for Ampicillin/Sulbactam Disk Diffusion and MIC Determinations

		Disk Diffusion	MIC
		(Zone diameter in mm)	(mcg/mL ampicillin/mcg/mL sulbactam)
<i>E. coli</i>	(ATCC 25922)	19–24	2/1–8/4
<i>S. aureus</i>	(ATCC 25923)	29–37	Not applicable
<i>E. coli</i>	(ATCC 35218)	13–19	8/4–32/16
<i>H. influenzae</i>	(ATCC 49247)	14–22	2/1–8/4

### INDICATIONS AND USAGE

Ampicillin and Sulbactam for Injection, USP is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below.

**Skin and Skin Structure Infections** caused by beta-lactamase producing strains of *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella* spp.\* (including *K. pneumoniae*), *Proteus mirabilis*, *Bacteroides fragilis*, *Enterobacter* spp.,\* and *Acinetobacter calcoaceticus*.\*

NOTE: For information on use in pediatric patients see **PRECAUTIONS – Pediatric Use** and **CLINICAL STUDIES** sections.

**Intra-Abdominal Infections** caused by beta-lactamase producing strains of *Escherichia coli*, *Klebsiella* spp. (including *K. pneumoniae*), *Bacteroides* spp. (including *B. fragilis*), and *Enterobacter* spp.\*

**Gynecological Infections** caused by beta-lactamase producing strains of *Escherichia coli*,\* and *Bacteroides* spp.\* (including *B. fragilis*).

\*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

While Ampicillin and Sulbactam for Injection, USP is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with Ampicillin and Sulbactam for Injection, USP due to its ampicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and beta-lactamase producing organisms susceptible to Ampicillin and Sulbactam for Injection, USP should not require the addition of another antibacterial.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify the organisms causing infection and to determine their susceptibility to Ampicillin and Sulbactam for Injection, USP.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies, when there is reason to believe the infection may involve any of the beta-lactamase producing organisms listed above in the indicated organ systems. Once the results are known, therapy should be adjusted if appropriate.

To reduce the development of drug-resistant bacteria and maintain effectiveness of Ampicillin and Sulbactam for Injection, USP and other antibacterial drugs, Ampicillin and Sulbactam for Injection, USP should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

### CONTRAINDICATIONS

The use of Ampicillin and Sulbactam for Injection is contraindicated in individuals with a history of serious hypersensitivity reactions (e.g., anaphylaxis or Stevens-Johnson syndrome) to ampicillin, sulbactam or to other beta-lactam antibacterial drugs (e.g., penicillins and cephalosporins).

Ampicillin and Sulbactam for Injection is contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with Ampicillin and Sulbactam for Injection.

### WARNINGS

#### Hypersensitivity

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, Ampicillin and Sulbactam for Injection should be discontinued and the appropriate therapy instituted.

#### Hepatotoxicity

Hepatic dysfunction, including hepatitis and cholestatic jaundice has been associated with the use of Ampicillin and Sulbactam for Injection. Hepatic toxicity is usually reversible; however, deaths have been reported. Hepatic function should be monitored at regular intervals in patients with hepatic impairment.

#### Severe Cutaneous Adverse Reactions

Ampicillin and Sulbactam for Injection may cause severe skin reactions, such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), dermatitis exfoliative, erythema multiforme, and acute generalized exanthematous pustulosis (AGEP). If patients develop a skin rash they should be monitored closely and Ampicillin and Sulbactam for Injection discontinued if lesions progress. (See *Contraindications and Adverse Reactions* sections.)

#### *Clostridium difficile*-Associated Diarrhea

*Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Ampicillin and Sulbactam for Injection, 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*.

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**Ampicillin and Sulbactam for Injection, USP**  
Rx Only

