FOR PROPER USE OF PHARMACY BULK PACKAGE
able parenteral fluids in the preparation of admixtures for intravenous infusion (see setting; it provides many single doses of ampicillin and sulbactam for injection for addition to suit-use that contains many single doses. The Pharmacy Bulk Package is for use in a pharmacy admixture (equivalent to 10 g ampicillin as the sodium salt plus 5 g sulbactam as the sodium salt). The sodium sulbactam sodium equivalent to 250 mg ampicillin per mL and 125 mg sulbactam per mL. The pH of soluble in aqueous diluents to yield pale yellow to yellow solutions containing ampicillin sodium and white dry powder for reconstitution. Ampicillin and Sulbactam for Injection, USP dry powder is freely

Ampicillin and Sulbactam for Injection, USP parenteral combination, is available as a white to off-

C8H10NNaO5S  M.W. 255.22

Sulbactam sodium is a derivative of the basic penicillin nucleus. Chemically, sulbactam sodium is

C16H18N3NaO4S  M.W. 371.39

Ampicillin and Sulbactam for Injection, USP is a sterile, injectable antibacterial combination consist-
ing of the semisynthetic antibiotic ampicillin sodium and the beta-lactamase inhibitor sulbactam sodium for parenteral administration. THE INTENT OF THIS PHARMACY BULK PACKAGE IS FOR PREPARATION OF SOLUTIONS FOR IV INFUSION ONLY.

Ampicillin sodium is derived from the penicillin nucleus, 6-aminopenicillanic acid. Chemically, it is monosodium (2S, 5R, 6R-6-[3(R)-2-amino-2-phenylacetamido]-3, 3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid) sodium, 2-hydroxy-2-carboxylate. The structural formula is:

\[
\text{C}_{16}\text{H}_{18}\text{N}_3\text{NaO}_4\text{S} \quad \text{M.W. 371.39}
\]

Subactam sodium is a derivative of the basic penicillin nucleus. Chemically, subactam sodium is sodium penicillinate sulfone; sodium (2S, 5R, 6R-6-[3(R)-2-amino-2-phenylacetamido]-3, 3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid) sodium. The structural formula is:

\[
\text{C}_{16}\text{H}_{18}\text{N}_3\text{NaO}_4\text{S} \quad \text{M.W. 255.22}
\]

Ampicillin and Sulbactam for Injection, USP parental combination, is available as a white to off-white 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 subactam per mL. The pH of the solutions is between 8 and 10. Dilute solutions (up to 30 mg ampicillin and 15 mg subactam per mL) are essentially colorless to pale yellow. The pH of dilute solutions remains the same.

Each sterile Pharmacy Bulk Package contains 15 grams Ampicillin and Sulbactam for Injection (equivalent to 10 g ampicillin as the sodium salt plus 5 g sulbactam as the sodium salt). The sodium content is 1195 mg (52.66 g) sodium. Ampicillin and Sulbactam for Injection Pharmacy Bulk Package is a vial containing a sterile preparation of ampicillin sodium and sulbactam sodium for parenteral use that contains many single doses. The Pharmacy Bulk Package is for use in a pharmacy admixture setting. It provides many single doses of ampicillin and sulbactam for injection for addition to suitable parenteral fluids in the preparation of admixtures for intravenous infusion (see DIRECTIONS FOR PROPER USE OF PHARMACY BULK PACKAGE). FURTHER DILUTION IS REQUIRED BEFORE USE.

CLINICAL PHARMACOLOGY:

Ampicillin and sulbactam extend the antibiotic spectrum of ampicillin to include many bacteria normally resistant to it and to organisms responsible for transferred drug resistance. Sulbactam has no effect on the activity of ampicillin against ampicillin susceptible susceptible strains. The presence of sulbactam in the Ampicillin and Sulbactam for Injection formulation effectively extends the antibiotic 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 antibiotic and a beta-lactamase inhibitor.

While in vitro studies have demonstrated the susceptibility of most strains of the following organ-
isms, clinical efficacy for infections other than those listed in the indications 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), Staphylococcus haemolyticus (heteroresistant), Streptococcus pneumoniae (formerly, S. pneumoniae), Streptococcus pyogenes, Streptococcus viridans.

Gram-Negative Bacteria

Haemophilus influenzae (beta-lactamase and non-beta-lactamase producing), Moraxella (Rhanilini) catarrhalis (beta-lactamase and non-beta-lactamase producing), Escherichia coli (beta-lactamase and non-beta-lactamase producing), Klebsiella pneumoniae (all known strains are beta-
lactamase producing), Proteus mirabilis (beta-lactamase and non-beta-lactamase producing),

DOSAGE AND ADMINISTRATION

General

Immediately after completion of a 15-minute intravenous infusion of Ampicillin and Sulbactam for Injection, peak serum concentrations of ampicillin and sulbactam are attained. Ampicillin serum lev-

ies 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 subactam and 40 to 71 mcg/mL after administration of 1000 mg ampicillin plus 500 mg subactam. The corresponding mean peak serum levels for subactam range from 48 to 88 mcg/mL, and 2 to 40 mcg/mL, respectively.

The mean serum half-life of both drugs is approximately 1 hour in healthy volunteers. Approximately 75 to 95% of both ampicillin and subactam are excreted unchanged in the urine during the first 8 hours after administration of Ampicillin and Sulbactam for Injection to individuals with normal renal function. Soms lower and more prolonged serum levels of ampicillin and sul-
bactam 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 fre-

Ampicillin and sulbactam are for the treatment of infections caused by bacteria.

Ampicillin sodium is derived from the penicillin nucleus, 6-aminopenicillanic acid. Chemically, it is monosodium (2S, 5R, 6R-6-[3(R)-2-amino-2-phenylacetamido]-3, 3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid) sodium, 2-hydroxy-2-carboxylate. The structural formula is:

\[
\text{C}_{16}\text{H}_{18}\text{N}_3\text{NaO}_4\text{S} \quad \text{M.W. 255.22}
\]

Ampicillin has a broad spectrum of bactericidal activity against many gram-positive and gram-nega-

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 gram-positive bacteria and in vitro studies have demonstrated the susceptibility of most strains of the following organ-
isms, clinical efficacy for infections other than those listed in the indications 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), Staphylococcus haemolyticus (heteroresistant), Streptococcus pneumoniae (formerly, S. pneumoniae), Streptococcus pyogenes, Streptococcus viridans.

Gram-Negative Bacteria

Haemophilus influenzae (beta-lactamase and non-beta-lactamase producing), Moraxella (Rhanilini) catarrhalis (beta-lactamase and non-beta-lactamase producing), Escherichia coli (beta-
lactamase and non-beta-lactamase producing), Klebsiella pneumoniae (all known strains are beta-
lactamase producing), Proteus mirabilis (beta-lactamase and non-beta-lactamase producing),
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.

**INDICATIONS AND USAGE:**

The use of Ampicillin and Sulbactam for Injection is contraindicated in individuals with a history of hypersensitivity reactions 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 severe 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. Serious anaphylactic reactions require immediate emergency treatment with epinephrine, hydrocortisone, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including Ampicillin and Sulbactam for injection, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that therapies produced by Clindamycin-resistant strains of *Clostridium difficile* are primary cause of “antibiotic-associated colitis.”

Mild cases of pseudomembranous colitis usually respond to discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

**PRECAUTIONS:**

**General:**

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin-class antibiotics should not be administered to patients with mononucleosis. In patients treated with ampicillin and sulbactam the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or Candida, the drug should be discontinued and/or appropriate therapy instituted.

Prescribing ampicillin and sulbactam in the absence of proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

**Information for Patients:**

Patients should be counseled that antibacterial drugs including ampicillin and sulbactam should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When antibacterial drugs are improperly used or administered, they maySelection of Drug for Use in Laboratory Tests Interactions

Administration of ampicillin and sulbactam will result in high urine concentration of ampicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of penicillin in urine samples.
of glucose in urine using Clinistix™, Benedict’s Solution or Fehling’s Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™ or Diastix™) be used. Allergic reactions include urticaria, rash, urticarial hives, and an occasional case of anaphylactoid reactions (see WARNINGS). The drug should be used during pregnancy only if clearly needed (see DRUG/LABORATORY TEST INTERACTIONS).

Adverse Reactions:

The safety and effectiveness of Ampicillin and Sulbactam for Injection have been established for pediatric patients 1 year of age or older for oral and intravenous use in skin and skin structure infections as approved in adults. Use of Ampicillin and Sulbactam for Injection in pediatric patients is supported by evidence from adequately and well-controlled studies in adults with additional data from pediatric pharmacokinetic studies, a controlled clinical trial conducted in pediatric patients, and post-marketing adverse events surveillance (see CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, and CLINICAL STUDIES).

The safety and effectiveness of Ampicillin and Sulbactam for Injection have not been established for pediatric patients for intra-abdominal infections.

ADVERSE REACTIONS:

Adult Patients

Ampicillin and Sulbactam for Injection is generally well tolerated. The following adverse reactions have been observed.

Allergic Reactions

Pain at injection site -3%

Systemic Reactions

Increased AST (SGOT), ALT (SGPT), alkaline phosphatase, and LDH.

Hepatic:

Decreased serum albumin and total proteins.

Neurological adverse reactions, including convulsions, may occur with the attainment of high CSF levels of beta-lactams. Ampicillin may be removed from circulation by hemodialysis. The molecular weight, degree of protein binding, and pharmacokinetics profile of sulbactam suggest that this compound may also be removed by hemodialysis.

CLINICAL STUDIES:

Skin and Skin Structure Infections in Pediatric Patients

Data from a controlled clinical trial conducted in pediatric patients provided evidence supporting the safety and efficacy of Ampicillin and Sulbactam for Injection for the treatment of skin and skin structure infections. Of 89 pediatric patients evaluated for clinical efficacy, 60 patients received a regimen containing intravenous Ampicillin and Sulbactam for Injection, and 39 patients received a regimen containing intravenous cefuroxime. This trial demonstrated similar outcomes (assessed at an appropriate interval after discontinuation of all antimicrobial therapy) for Ampicillin and Sulbactam for Injection and cefuroxime-treated patients.

Therapeutic Regimen

Ampicillin and Sulbactam for Injection

Cefuroxime

Gentamicin

Ceftriaxone

Clinical Failure

51/60 (85%)

9/40 (10%)

34/39 (87%)

5/39 (13%)

Most patients received a course of oral antimicrobials following initial treatment with intravenous administration of parenteral antimicrobial drugs. The study protocol required that the following three criteria be met prior to transition from intravenous to oral antimicrobial therapy: 1) receipt of a minimum of 72 hours of intravenous therapy; 2) no documented fever for prior 24 hours; and 3) improvement or resolution of all signs and symptoms of infection.

The choice of oral antimicrobial agent used in this trial was determined by susceptibility testing of the original pathogens, if isolated, to oral agents available. The course of oral antimicrobial therapy should not routinely exceed 14 days.

DOSAGE AND ADMINISTRATION:

Ampicillin and Sulbactam for Injection, USP may be used for parenteral administration (following dilution). THE INTENT OF THIS PHARMACY BULK PACKAGE IS FOR PREPARATION OF SOLUTIONS FOR IV INFUSION ONLY.

For IV administration, the dose can be given by slow intravenous injection over at least 10 to 15 minutes or can also be delivered, in greater dilutions with 50 to 100 mL of a compatible diluent as an intravenous infusion over 15 to 30 minutes.

The recommended adult dosage of ampicillin and sulbactam is 1.5 g (1 g ampicillin as the sodium salt plus 0.5 g sulbactam as the sodium salt) to 2 g (1 g ampicillin as the sodium salt plus 1 g sulbactam as the sodium salt) per day. This 1.5 to 2 g range represents the total amount of ampicillin content plus the sulbactam content of Ampicillin and Sulbactam for Injection. If the patient requires a range of 1 g ampicillin/0.5 g sulbactam to 2 g ampicillin/1 g sulbactam, the total dose of sulbactam should not exceed 4 grams per day.

Pediatric Patients: 5 Years of Age or Older

The recommended daily dose of Ampicillin and Sulbactam for Injection, USP in pediatric patients is 300 mg per kg of body weight administered intravenously in equally divided doses every 6 hours. This 300 mg/kg/day dosage represents the total ampicillin content plus the sulbactam content of Ampicillin and Sulbactam for Injection, and corresponds to 100 mg ampicillin/100 mg sulbactam per kg per day. Pediatric patients weighing 40 kg or more should be dosed according to adult recommendations, and the total dose of sulbactam should not exceed 4 grams per day. The course of intravenous therapy should not routinely exceed 14 days. In clinical trials, most children received a course of oral antimicrobials following initial treatment with intravenous Ampicillin and Sulbactam for Injection, USP (see CLINICAL STUDIES).

Impaired Renal Function

In patients with impairment of 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 fre-
Ampicillin and Sulbactam for Injection, USP

Dosage Guide For Patients With Renal Impairment

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min/1.73m²)</th>
<th>Ampicillin/Sulbactam Half-Life (Hours)</th>
<th>Recommended Ampicillin and Sulbactam for Injection, USP</th>
<th>Doseage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30</td>
<td>1</td>
<td>1.5 to 3 g q8h - q12h</td>
<td>5 to 14</td>
</tr>
<tr>
<td>15 to 20</td>
<td>5</td>
<td>1.5 to 3 g q12h</td>
<td></td>
</tr>
<tr>
<td>5 to 14</td>
<td>9</td>
<td>1.5 to 3 g q24h</td>
<td></td>
</tr>
</tbody>
</table>

When only serum creatinine is available, the following formula (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

Males: weight (kg) x (140 – age) / 72 x serum creatinine

Females: 0.85 x above value

COMPATIBILITY, RECONSTITUTION AND STABILITY:

When coadministration with aminoglycosides is indicated, Ampicillin and Sulbactam for injection and aminoglycosides should be reconstituted and administered separately, due to the in vivo interaction of aminoglycosides by any of the aminopenicillins.

DIRECTIONS FOR USE:

General Reconstitution Procedures

Ampicillin and Sulbactam for Injection, USP sterile powder for intravenous use may be reconstituted with any of the compatible diluents described in this insert. Solutions should be allowed to stand after dissolution to allow any foam to dissipate in order to permit visual inspection for complete solubilization.

Preparation for Intravenous Use

After reconstitution of the Pharmacy Bulk Package, an appropriate volume should then be immediately diluted with a suitable parenteral diluent to yield solutions containing a concentration 3 and 45 mg (2 to 30 mg ampicillin/1 to 15 mg sulbactam/mL). The closure may be penetrated only one time after reconstitution, if needed, using a suitable sterile transfer device or dispensing set which allows measured dispensing of the contents.

After reconstitution, use within two hours if stored at room temperature, or within four hours if stored under refrigeration.

Reconstituted Bulk Solution Should Not Be Used for Direct Infusion

If the reconstituted bulk solution is stored for less than one hour at room temperature (20° to 25°C) prior to further dilution, the use periods indicated in Table A apply for the diluted solutions.

If the bulk solution is stored for one to two hours at room temperature (20°C to 25°C) and then diluted with Sterile Water for Injection or 0.9% Sodium Chloride Injection to the following concentrations, the use periods indicated in Table B apply. Any unused portions of solution that remain after the indicated time periods should be discarded.

### Table B

<table>
<thead>
<tr>
<th>IV Solution</th>
<th>Maximum Concentration (mg/mL)</th>
<th>Use Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterile Water for Injection, USP</td>
<td>45 (30/15)</td>
<td>4 hrs @ 21°C</td>
</tr>
<tr>
<td>0.9% Sodium Chloride Injection, USP</td>
<td>45 (30/15)</td>
<td>4 hrs @ 21°C</td>
</tr>
</tbody>
</table>

Animal Pharmacology

While reversible glycosgenosis was observed in laboratory animals, this phenomenon was dose- and time-dependent and is not expected to develop at the therapeutic doses and corresponding plasma levels attained during the relatively short periods of combined ampicillin/sulbactam therapy in man.

HOW SUPPLIED:

Ampicillin and Sulbactam for Injection, USP, a sterile off-white dry powder, is available in the Pharmacy Bulk Package containing ampicillin sodium and sulbactam sodium equivalent to 10 g ampicillin and 5 g sulbactam.

<table>
<thead>
<tr>
<th>Product No.</th>
<th>NDC No.</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>303620</td>
<td>63323-368-30</td>
<td>1.5 grams</td>
</tr>
<tr>
<td>306200</td>
<td>63323-369-30</td>
<td>3 grams</td>
</tr>
</tbody>
</table>

Packaged individually.

Ampicillin and Sulbactam for Injection, USP powder is to be stored at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature], prior to reconstitution.

Ampicillin and Sulbactam for Injection, USP is also available as:

<table>
<thead>
<tr>
<th>Product No.</th>
<th>NDC No.</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>307662</td>
<td>63323-370-62</td>
<td>15 grams</td>
</tr>
</tbody>
</table>

Packaged in tens.

### REFERENCES:


### Table A

<table>
<thead>
<tr>
<th>Diluent</th>
<th>Maximum Concentration (mg/mL)</th>
<th>Use Periods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterile Water for Injection, USP</td>
<td>45 (30/15)</td>
<td>8 hrs @ 21°C</td>
</tr>
<tr>
<td>0.9% Sodium Chloride Injection, USP</td>
<td>45 (30/15)</td>
<td>48 hrs @ 4°C</td>
</tr>
<tr>
<td>0.9% Dextrose Injection</td>
<td>30 (20/10)</td>
<td>2 hrs @ 21°C</td>
</tr>
<tr>
<td>Lactated Ringer's Injection</td>
<td>45 (30/15)</td>
<td>12 hrs @ 4°C</td>
</tr>
<tr>
<td>M/S Sodium Lactate Injection</td>
<td>45 (30/15)</td>
<td>24 hrs @ 4°C</td>
</tr>
<tr>
<td>5% Dextrose in 0.45% Saline</td>
<td>3 (21)</td>
<td>4 hrs @ 23°C</td>
</tr>
<tr>
<td>10% Invert Sugar</td>
<td>3 (21)</td>
<td>4 hrs @ 23°C</td>
</tr>
</tbody>
</table>