**70-4361-44-3.1**

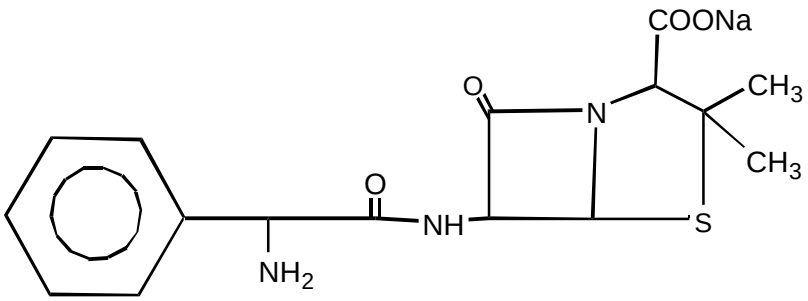
# UNASYN®
## (ampicillin sodium/sulbactam sodium)

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

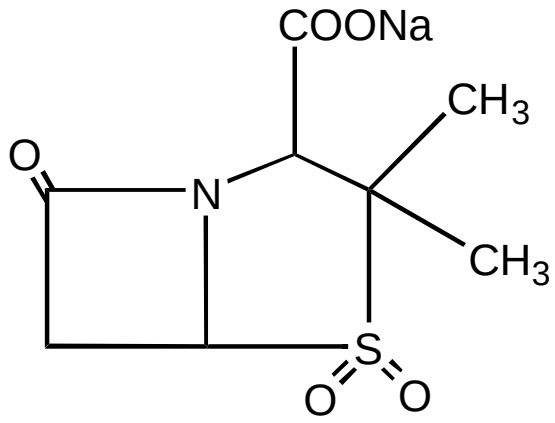
### DESCRIPTION

UNASYN is an injectable antibacterial combination consisting of the semisynthetic antibiotic 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 $C_8H_{10}NNaO_5S$ with a molecular weight of 255.22. The structural formula is:




UNASYN, ampicillin sodium/sulbactam sodium parenteral combination, is available as a white to off-white dry powder for reconstitution. UNASYN 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 8.0 and 10.0.

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.

1.5 g of UNASYN (1 g ampicillin as the sodium salt plus 0.5 g sulbactam as the sodium salt) parenteral contains approximately 115 mg (5 mEq) of sodium.

3 g of UNASYN (2 g ampicillin as the sodium salt plus 1 g sulbactam as the sodium salt) parenteral contains approximately 230 mg (10 mEq) of sodium.

## CLINICAL PHARMACOLOGY

**General:** Immediately after completion of a 15-minute intravenous infusion of UNASYN, 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 UNASYN 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 UNASYN 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 A**
**Concentration of UNASYN 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 UNASYN.

The pharmacokinetics of ampicillin and sulbactam in pediatric patients receiving UNASYN are similar to those observed in adults. Immediately after a 15-minute infusion of 50 to 75 mg UNASYN/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 UNASYN formulation effectively extends the antibiotic spectrum of ampicillin to include many bacteria normally resistant to it and to other beta-lactam antibiotics. Thus, UNASYN 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 organisms, clinical efficacy for infections other than those included 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), *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 Kirby-Bauer method of susceptibility testing, a 20 mcg (10 mcg ampicillin + 10 mcg sulbactam) diffusion disk should be used. The method is one outlined in the NCCLS publication M2-A4.[1] With this procedure, a report from the laboratory of "Susceptible" indicates that the infecting organism is likely to respond to UNASYN 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 UNASYN if a higher dosage is used or if the infection is confined to tissues or fluids (e.g., urine) in which high antibiotic levels are attained.

**Dilution Techniques:** Broth or agar dilution methods may be used to determine the minimal inhibitory concentration (MIC) value for susceptibility of bacterial isolates to ampicillin/ sulbactam. The method used is one outlined in the NCCLS publication M7-A2.[2] Tubes should be inoculated to contain $10^5$ to $10^6$ organisms/mL or plates "spotted" with $10^4$ organisms.

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.

**Recommended ampicillin/sulbactam, Susceptibility Ranges[1,2,3]**

| | Resistant | Intermediate | Susceptible |
|---|---|---|---|
| *Gram(-) and Staphylococcus* | | | |
| Bauer/Kirby Zone Sizes | ≤11 mm | 12-13 mm | ≥14 mm |
| MIC (mcg of ampicillin/mL) | ≥32 | 16 | ≤ 8 |
| *Hemophilus influenzae* | | | |
| Bauer/Kirby Zone Sizes | ≤19 | — | ≥20 |
| MIC (mcg of ampicillin/mL) | ≥ 4 | — | ≤ 2 |

[1]The non-beta-lactamase producing organisms which are normally susceptible to ampicillin, such as *Streptococci*, will have similar zone sizes as for ampicillin disks.
[2]*Staphylococci* resistant to methicillin, oxacillin, or nafcillin must be considered resistant to UNASYN.
[3]The quality control cultures should have the following assigned daily ranges for ampicillin/sulbactam:

| | | **Disks** | **Mode MIC (mcg/mL ampicillin/ mcg/mL sulbactam)** |
|---|---|---|---|
| *E. coli* | (ATCC 25922) | 20-24 mm | 2/1 |
| *S. aureus* | (ATCC 25923) | 29-37 mm | 0.12/0.06 |
| *E. coli* | (ATCC 35218) | 13-19 mm | 8/4 |

## INDICATIONS AND USAGE

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

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 UNASYN.

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 UNASYN and other antibacterial drugs, UNASYN should be used only to treat or prevent 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 UNASYN 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 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, UNASYN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

**Pseudomembranous colitis has been reported with nearly all antibacterial agents, including UNASYN, 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 toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

Mild cases of pseudomembranous colitis usually respond to drug 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 UNASYN 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 UNASYN 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 UNASYN should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When UNASYN is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by UNASYN or other antibacterial drugs in the future.

**Drug Interactions:** Probenecid decreases the renal tubular secretion of ampicillin and sulbactam. Concurrent use of probenecid with UNASYN may result in increased and prolonged blood levels of ampicillin and sulbactam. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients

receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with UNASYN and allopurinol administered concurrently. UNASYN and aminoglycosides should not be reconstituted together due to the *in vitro* inactivation of aminoglycosides by the ampicillin component of UNASYN.

**Drug/Laboratory Test Interactions:** Administration of UNASYN 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 glucose in urine using Clinitest™, Benedict's Solution or Fehling's Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™ or Testape™) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone and estradiol has been noted. This effect may also occur with UNASYN.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

**Pregnancy**
**Pregnancy Category B:** Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to UNASYN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (See– Drug/Laboratory Test Interactions.)

**Labor and Delivery:** Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of UNASYN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

**Nursing Mothers:** Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore, caution should be exercised when UNASYN is administered to a nursing woman.

**Pediatric Use:** The safety and effectiveness of UNASYN have been established for pediatric patients one year of age and older for skin and skin structure infections as approved in adults. Use of UNASYN in pediatric patients is supported by evidence from adequate 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** sections.)

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

## ADVERSE REACTIONS

**Adult Patients:** UNASYN is generally well tolerated. The following adverse reactions have been reported.

**Local Adverse Reactions**
Pain at IM injection site – 16%
Pain at IV injection site – 3%
Thrombophlebitis – 3%

**Systemic Adverse Reactions**
The most frequently reported adverse reactions were diarrhea in 3% of the patients and rash in less than 2% of the patients.

Additional systemic reactions reported in less than 1% of the patients were: itching, nausea, vomiting, candidiasis, fatigue, malaise, headache, chest pain, flatulence, abdominal distension, glossitis, urine retention, dysuria, edema, facial swelling, erythema, chills, tightness in throat, substernal pain, epistaxis and mucosal bleeding.

**Pediatric Patients:** Available safety data for pediatric patients treated with UNASYN demonstrate a similar adverse events profile to those observed in adult patients. Additionally, atypical lymphocytosis has been observed in one pediatric patient receiving UNASYN.

**Adverse Laboratory Changes**
Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:

*Hepatic:* Increased AST (SGOT), ALT (SGPT), alkaline phosphatase, and LDH.
*Hematologic:* Decreased hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, platelets and increased lymphocytes, monocytes, basophils, eosinophils, and platelets.
*Blood Chemistry:* Decreased serum albumin and total proteins.
*Renal:* Increased BUN and creatinine.
*Urinalysis:* Presence of RBC's and hyaline casts in urine.

The following adverse reactions have been reported with ampicillin-class antibiotics and can also occur with UNASYN.

**Gastrointestinal:** Gastritis, stomatitis, black "hairy" tongue and enterocolitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS.)

**Hypersensitivity Reactions:** Urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with a penicillin. (See WARNINGS.)

**Hematologic:** In addition to the adverse laboratory changes listed above for UNASYN, agranulocytosis has been reported during therapy with penicillins. All of these reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. Some individuals have developed positive direct Coombs Tests during treatment with UNASYN, as with other beta-lactam antibiotics.

## OVERDOSAGE

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 UNASYN for the treatment of skin and skin structure infections. Of 99 pediatric patients evaluable for clinical efficacy, 60 patients received a regimen containing intravenous UNASYN, 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 UNASYN- and cefuroxime-treated patients:

| Therapeutic Regimen | Clinical Success | Clinical Failure |
|---|---|---|
| UNASYN | 51/60 (85%) | 9/60 (15%) |
| Cefuroxime | 34/39 (87%) | 5/39 (13%) |

Most patients received a course of oral antimicrobials following initial treatment with intravenous administration of parenteral antimicrobials. 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 the signs and symptoms of infection.

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

## DOSAGE AND ADMINISTRATION

UNASYN may be administered by either the IV or the IM routes.

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

UNASYN may be administered by deep intramuscular injection. (See Preparation for Intramuscular Injection.)

The recommended adult dosage of UNASYN is 1.5 g (1 g ampicillin as the sodium salt plus 0.5 g sulbactam as the sodium salt) to 3 g (2 g ampicillin as the sodium salt plus 1 g sulbactam as the sodium salt) every six hours. This 1.5 to 3 g range represents the total of ampicillin content plus the sulbactam content of UNASYN, and corresponds to 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 1 Year of Age or Older:** The recommended daily dose of UNASYN in pediatric patients is 300 mg per kg of body weight administered via intravenous infusion in equally divided doses every 6 hours. This 300 mg/kg/day dosage represents the total ampicillin content plus the sulbactam content of UNASYN, and corresponds to 200 mg ampicillin/100 mg sulbactam per kg per day. The safety and efficacy of UNASYN administered via intramuscular injection in pediatric patients have not been established. 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 UNASYN. (See **CLINICAL STUDIES** section.)

### 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 UNASYN in such patients should be administered less frequently in accordance with the usual practice for ampicillin and according to the following recommendations:

**UNASYN Dosage Guide For Patients With Renal Impairment**

| Creatinine Clearance ($mL/min/1.73m^2$) | Ampicillin/Sulbactam Half-Life (Hours) | Recommended UNASYN Dosage |
|---|---|---|
| ≥30 | 1 | 1.5-3.0 g q 6h-q 8h |
| 15-29 | 5 | 1.5-3.0 g q 12h |
| 5-14 | 9 | 1.5-3.0 g q 24h |

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 $\frac{\text{weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine}}$

Females $0.85 \times$ above value

## COMPATIBILITY, RECONSTITUTION AND STABILITY

UNASYN sterile powder is to be stored at or below 30°C (86°F) prior to reconstitution.

When concomitant therapy with aminoglycosides is indicated, UNASYN and aminoglycosides should be reconstituted and administered separately, due to the *in vitro* inactivation of aminoglycosides by any of the aminopenicillins.

## DIRECTIONS FOR USE

**General Dissolution Procedures:** UNASYN sterile powder for intravenous and intramuscular 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 foaming to dissipate in order to permit visual inspection for complete solubilization.

**Preparation for Intravenous Use**

1.5 g and 3.0 g Bottles: UNASYN sterile powder in piggyback units may be reconstituted directly to the desired concentrations using any of the following parenteral diluents. Reconstitution of UNASYN, at the specified concentrations, with these diluents provide stable solutions for the time periods indicated in the following table: (After the indicated time periods, any unused portions of solutions should be discarded.)

| Diluent | Maximum Concentration (mg/mL) UNASYN (Ampicillin/Sulbactam) | Use Periods |
|---|---|---|
| Sterile Water for Injection | 45 (30/15) | 8 hrs @25°C |
| | 45 (30/15) | 48 hrs @ 4°C |
| | 30 (20/10) | 72 hrs @ 4°C |
| 0.9% Sodium Chloride Injection | 45 (30/15) | 8 hrs @25°C |
| | 45 (30/15) | 48 hrs @ 4°C |
| | 30 (20/10) | 72 hrs @ 4°C |
| 5% Dextrose Injection | 30 (20/10) | 2 hrs @25°C |
| | 30 (20/10) | 4 hrs @ 4°C |
| | 3 (2/1) | 4 hrs @25°C |
| Lactated Ringer's Injection | 45 (30/15) | 8 hrs @25°C |
| | 45 (30/15) | 24 hrs @ 4°C |
| M/6 Sodium Lactate Injection | 45 (30/15) | 8 hrs @25°C |
| | 45 (30/15) | 8 hrs @ 4°C |
| 5% Dextrose in 0.45% Saline | 3 (2/1) | 4 hrs @25°C |
| | 15 (10/5) | 4 hrs @ 4°C |
| 10% Invert Sugar | 3 (2/1) | 4 hrs @25°C |
| | 30 (20/10) | 3 hrs @ 4°C |

If piggyback bottles are unavailable, standard vials of UNASYN sterile powder may be used. Initially, the vials may be reconstituted with Sterile Water for Injection to yield solutions containing 375 mg UNASYN per mL (250 mg ampicillin/125 mg sulbactam per mL). An appropriate volume should then be immediately diluted with a suitable parenteral diluent to yield solutions containing 3 to 45 mg UNASYN per mL (2 to 30 mg ampicillin/1 to 15 mg sulbactam/per mL).

1.5 g ADD-Vantage® Vials: UNASYN in the ADD-Vantage® system is intended as a single dose for intravenous administration after dilution with the ADD-Vantage® Flexible Diluent Container containing 50 mL, 100 mL or 250 mL of 0.9% Sodium Chloride Injection, USP.

3 g ADD-Vantage® Vials: UNASYN in the ADD-Vantage® system is intended as a single dose for intravenous administration after dilution with the ADD-Vantage® Flexible Diluent Container containing 100 mL or 250 mL of 0.9% Sodium Chloride Injection, USP.

UNASYN in the ADD-Vantage® system is to be reconstituted with 0.9% Sodium Chloride Injection, USP only. See INSTRUCTIONS FOR USE OF THE ADD-Vantage® VIAL. Reconstitution of UNASYN, at the specified concentration, with 0.9% Sodium Chloride Injection, USP provides stable solutions for the time period indicated below:

| Diluent | Maximum Concentration (mg/mL) UNASYN (Ampicillin/Sulbactam) | Use Period |
|---|---|---|
| 0.9% Sodium Chloride Injection | 30 (20/10) | 8 hrs @ 25°C |

**In 0.9% Sodium Chloride Injection, USP**
The final diluted solution of UNASYN should be completely administered *within 8 hours* in order to assure proper potency.

**Preparation for Intramuscular Injection**
**1.5 g and 3.0 g Standard Vials:** 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). Note: *Use only freshly prepared solutions and administer within one hour after preparation.*

| UNASYN Vial Size | Volume of Diluent to be Added | Withdrawal Volume* |
|---|---|---|
| 1.5 g | 3.2 mL | 4.0 mL |
| 3.0 g | 6.4 mL | 8.0 mL |

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

**Animal Pharmacology:** While reversible glycogenosis 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

UNASYN® (ampicillin sodium/sulbactam sodium) is supplied as a sterile off-white dry powder in glass vials and piggyback bottles. The following packages are available:

Vials containing 1.5 g (NDC 0049-0013-83) equivalent of UNASYN (1 g ampicillin as the sodium salt plus 0.5 g sulbactam as the sodium salt)

Vials containing 3 g (NDC 0049-0014-83) equivalent of UNASYN (2 g ampicillin as the sodium salt plus 1 g sulbactam as the sodium salt)

Bottles containing 1.5 g (NDC 0049-0022-83) equivalent of UNASYN (1 g ampicillin as the sodium salt plus 0.5 g sulbactam as the sodium salt)

Bottles containing 3 g (NDC 0049-0023-83) equivalent of UNASYN (2 g ampicillin as the sodium salt plus 1 g sulbactam as the sodium salt)

Pharmacy Bulk Package containing 15 g (NDC 0049-0024-28) equivalent of UNASYN (10 g ampicillin as the sodium salt plus 5 g sulbactam as the sodium salt)

ADD-Vantage® vials containing 1.5 g (NDC 0049-0031-83) equivalent of UNASYN (1 g ampicillin as the sodium salt plus 0.5 g sulbactam as the sodium salt) are distributed by Pfizer Inc.

ADD-Vantage® vials containing 3 g (NDC 0049-0032-83) equivalent of UNASYN (2 g ampicillin as the sodium salt plus 1 g sulbactam as the sodium salt) are distributed by Pfizer Inc.

The 1.5 g UNASYN ADD-Vantage® vials are only to be used with Abbott Laboratories' ADD-Vantage® Flexible Diluent Container containing 0.9% Sodium Chloride Injection, USP, 50 mL, 100 mL, or 250 mL sizes.

The 3 g UNASYN ADD-Vantage® vials are only to be used with Abbott Laboratories' ADD-Vantage® Flexible Diluent Container containing 0.9% Sodium Chloride Injection, USP, 100 mL or 250 mL sizes.

## INSTRUCTIONS FOR USE OF THE ADD-Vantage® VIAL

**To Open Diluent Container:** Peel overwrap from the corner and remove container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

**To Assemble Vial and Flexible Diluent Container: (Use Aseptic Technique)**

1. Remove the protective covers from the top of the vial and the vial port on the diluent container as follows:

a. To remove the breakaway vial cap, swing the pull ring over the top of the vial and pull down far enough to start the opening (see Figure 1), pull the ring approximately half way around the cap and then pull straight up to remove the cap (see Figure 2).

NOTE: Do not access vial with syringe.

**Fig. 1**

**Fig. 2**

b. To remove the vial port cover, grasp the tab on the pull ring, pull up to break the three tie strings, then pull back to remove the cover. (See Figure 3.)

2. Screw the vial into the vial port until it will go no further. THE VIAL MUST BE SCREWED IN TIGHTLY TO ASSURE A SEAL. This occurs approximately 1/2 turn (180°) after the first audible click. (See Figure 4.) The clicking sound does not assure a seal, the vial must be turned as far as it will go.

NOTE: Once vial is sealed, do not attempt to remove. (See Figure 4.)

3. Recheck the vial to assure that it is tight by trying to turn it further in the direction of assembly.

4. Label appropriately.

**Fig. 3**

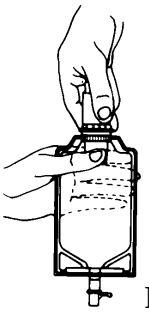


**Fig. 4**

**To Prepare Admixture**

1. Squeeze the bottom of the diluent container gently to inflate the portion of the container surrounding the end of the drug vial.

2. With the other hand, push the drug vial down into the container telescoping the walls of the container. Grasp the inner cap of the vial through the walls of the container. (See Figure 5.)

3. Pull the inner cap from the drug vial. (See Figure 6.) Verify that the rubber stopper has been pulled out, allowing the drug and diluent to mix.

4. Mix container contents thoroughly and use within the specified time.

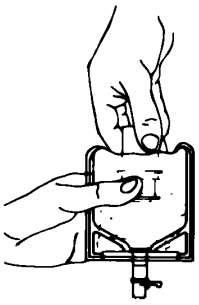


**Fig. 5**

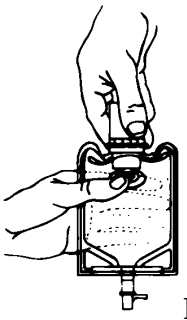


**Fig. 6**

## REFERENCES


1. National Committee for Clinical Laboratory Standards, *Performance Standards for Antimicrobial Disk Susceptibility Tests*–Fourth Edition. Approved Standard NCCLS Document M2-A4, Vol. 10, No. 7 NCCLS, Villanova, PA, April 1990.

2. National Committee for Clinical Laboratory Standards, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*, Second Edition. Approved Standard NCCLS Document M7-A2, Vol. 10, No. 8 NCCLS, Villanova, PA, April 1990.


**Rx only**

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