UNASYN- ampicillin sodium and sulbactam sodium injection, powder, for solution
Roerig

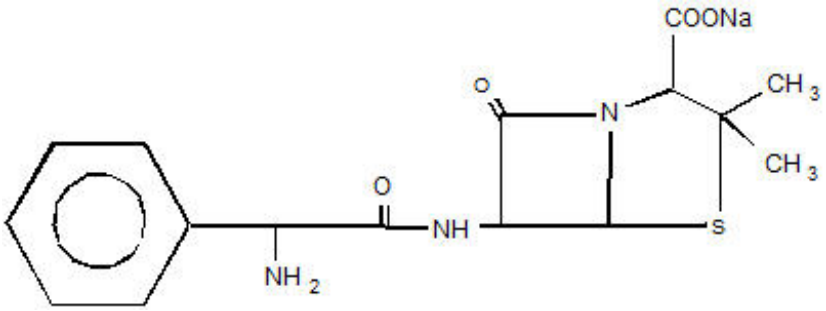
UNASYN®
(ampicillin sodium/sulbactam sodium)

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 infections that are proven or strongly suspected to be caused by bacteria.

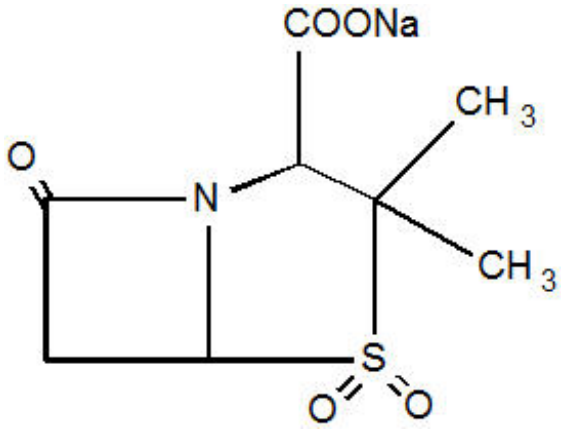
DESCRIPTION

UNASYN 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 $C_8H_{10}NNaO_5S$ 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** section).

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 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 antibacterial spectrum of ampicillin to include many bacteria normally resistant to it and

to other beta-lactam antibacterials. Thus, UNASYN 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*[1] (Enterococcus), *Streptococcus pneumoniae*[1] (formerly *D. pneumoniae*), *Streptococcus pyogenes*[1], *Streptococcus viridans*[1].

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,[1] *Peptococcus* species,[1] *Peptostreptococcus* species, *Bacteroides* species, including *B. fragilis*.

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

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

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*,[2] *Klebsiella* spp.[2] (including *K. pneumoniae*[2]), *Proteus mirabilis*,[2] *Bacteroides fragilis*,[2] *Enterobacter* spp.,[2] and *Acinetobacter calcoaceticus.*[2]

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*[2]), *Bacteroides* spp. (including *B.*

fragilis), and *Enterobacter* spp.[2]

Gynecological Infections caused by beta-lactamase producing strains of *Escherichia coli,*[2] and *Bacteroides* spp.[2] (including *B. fragilis*[2]).

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 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 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 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.

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

CONTRAINDICATIONS

The use of UNASYN 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).

UNASYN is contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with UNASYN.

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, UNASYN should be discontinued and the

appropriate therapy instituted.

Hepatotoxicity

Hepatic dysfunction, including hepatitis and cholestatic jaundice has been associated with the use of UNASYN. 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

UNASYN 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 UNASYN 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 UNASYN, 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 antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

General

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibacterial 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.

Diarrhea is a common problem caused by antibacterial which usually ends when the antibacterial is discontinued. Sometimes after starting treatment with antibacterial, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibacterial. If this occurs, patients should contact their physician as soon as possible.

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

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 –**PRECAUTIONS-Drug/Laboratory Test Interactions** section).

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 in clinical trials.

Local Adverse Reactions

Pain at IM injection site – 16%
Pain at IV injection site – 3%
Thrombophlebitis – 3%
Phlebitis – 1.2%

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.

Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following have been identified during post-marketing use of ampicillin sodium/sulbactam sodium or other products containing ampicillin. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency, or potential causal connection to ampicillin sodium/sulbactam sodium.

Blood and Lymphatic System Disorders: Hemolytic anemia, thrombocytopenic purpura, and agranulocytosis have been reported. 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 antibacterials.

Gastrointestinal Disorders: Abdominal pain, cholestatic hepatitis, cholestasis, hyperbilirubinemia, jaundice, abnormal hepatic function, melena, gastritis, stomatitis, dyspepsia, black "hairy" tongue, and *Clostridium difficile* associated diarrhea (see **CONTRAINDICATIONS** and **WARNINGS** sections).

General Disorders and Administration Site Conditions: Injection site reaction

Immune System Disorders: Serious and fatal hypersensitivity (anaphylactic) reactions (see **WARNINGS** section), Acute myocardial ischemia with or without myocardial infarction may occur as part of an allergic reaction.

Nervous System Disorders: Convulsion and dizziness

Renal and Urinary Disorders: Tubulointerstitial nephritis

Respiratory, Thoracic and Mediastinal Disorders: Dyspnea

Skin and Subcutaneous Tissue Disorders: Toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, Acute generalized exanthematous pustulosis (AGEP), erythema multiforme, exfoliative dermatitis, and urticaria (see **CONTRAINDICATIONS** and **WARNINGS** sections).

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:

TABLE 2

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 **DIRECTIONS FOR USE-Preparation for Intramuscular Injection** section).

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:

TABLE 3 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 g q 6h–q 8h
15–29	5	1.5–3 g q 12h
5–14	9	1.5–3 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 × 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).

TABLE 4

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

	30 (20/10)	3 hrs at 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 section. Reconstitution of UNASYN, at the specified concentration, with 0.9% Sodium Chloride Injection, USP provides stable solutions for the time period indicated below:

TABLE 5

Diluent	Maximum Concentration (mg/mL) UNASYN (Ampicillin/Sulbactam)	Use Period
0.9% Sodium Chloride Injection (USP)	30 (20/10)	8 hrs at 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.*

TABLE 6

UNASYN Vial Size	Volume of Diluent	Withdrawal

UNASYN Vial Size	to be Added	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).

ADD-Vantage® package of 5 vials (NDC 0049-0031-02). Each vial containing 1.5 g (NDC 0049-0031-01) 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® package of 5 vials (NDC 0049-0032-02). Each vial containing 3 g (NDC 0049-0032-01) 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 the 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 the ADD-Vantage® Flexible Diluent Container containing 0.9% Sodium Chloride Injection, USP, 100 mL or 250 mL sizes.

ADD-Vantage® is a registered trademark of Hospira Inc., a Pfizer company.

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.

Figure 1

Figure 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.

Figure 3

Figure 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.

Figure 5

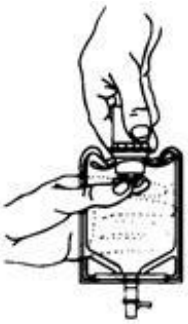


Figure 6

To report SUSPECTED ADVERSE EVENTS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or http://www.fda.gov/ for voluntary reporting of adverse reactions.

This product's labeling may have been updated. For the most recent prescribing information, please visit www.pfizer.com.

Pfizer Injectables

Distributed by
Roerig
Division of Pfizer Inc
New York, NY 10017

LAB-0017-20.0
Revised October 2020

PRINCIPAL DISPLAY PANEL - 1.5 g Injection Vial Label

NDC 0049-0013-81
Rx only

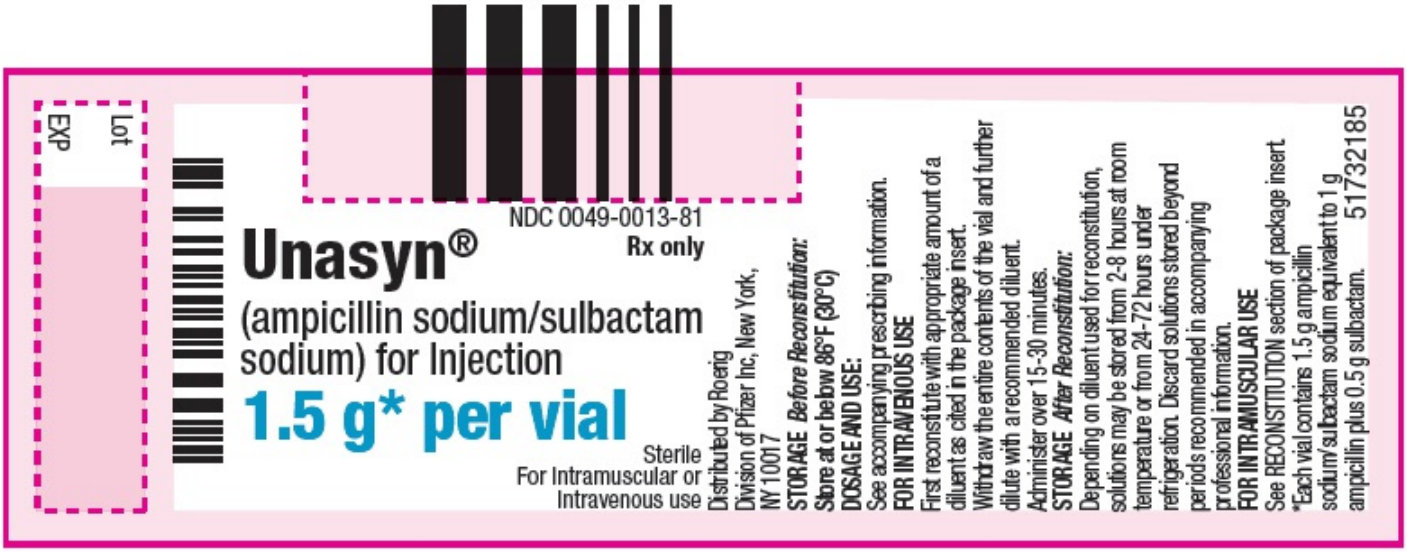
Unasyn®

(ampicillin sodium/sulbactam
sodium) for Injection

1.5 g* per vial

Sterile
For Intramuscular or
Intravenous use

XXXIII



PRINCIPAL DISPLAY PANEL - 1.5 g Vial Carton

NDC 0049-0013-83
contains 10 of NDC 0049-0013-81

Rx only

10 Vials

Unasyn®
(ampicillin sodium/sulbactam sodium)
for Injection

1.5 g* per vial

Sterile

For Intramuscular or Intravenous use

Pfizer Injectables

S5X10REV

10 Vials

NDC 0049-0013-83
contains 10 of NDC 0049-0013-81

Rx only

Unasyn®

(ampicillin sodium/sulbactam sodium)
for Injection

1.5 g* per vial

Sterile

For Intramuscular or Intravenous use

Pfizer Injectables

10 Vials

Unasyn®
(ampicillin sodium/
sulbactam sodium)
for Injection

1.5 g*
per vial

Sterile

For Intramuscular or Intravenous use

10 Vials

Unasyn®
(ampicillin sodium/sulbactam sodium)
for Injection

1.5 g* per vial

Sterile

For Intramuscular or Intravenous use

Pfizer Injectables

51743797
1.5IMIVIFC

STORAGE
Before Reconstitution:
Store at or below 86°F (30°C)

DOSAGE AND USE:
See accompanying prescribing information.
* Each vial contains 1.5 g ampicillin sodium/sulbactam sodium equivalent to 1 g ampicillin plus 0.5 g sulbactam.

MADE IN SPAIN

Distributed by
Roerig
Division of Pfizer Inc
New York, NY 10017

N 3 0049-0013-83 3

GTIN: 00300490013833
Lot
EXP

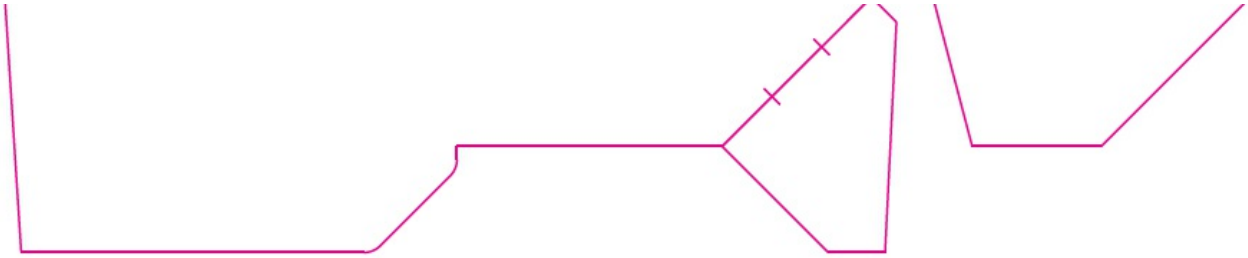
10 Vials

Unasyn®
(ampicillin sodium/
sulbactam sodium)
for Injection

1.5 g*
per vial

Sterile

For Intramuscular or Intravenous use



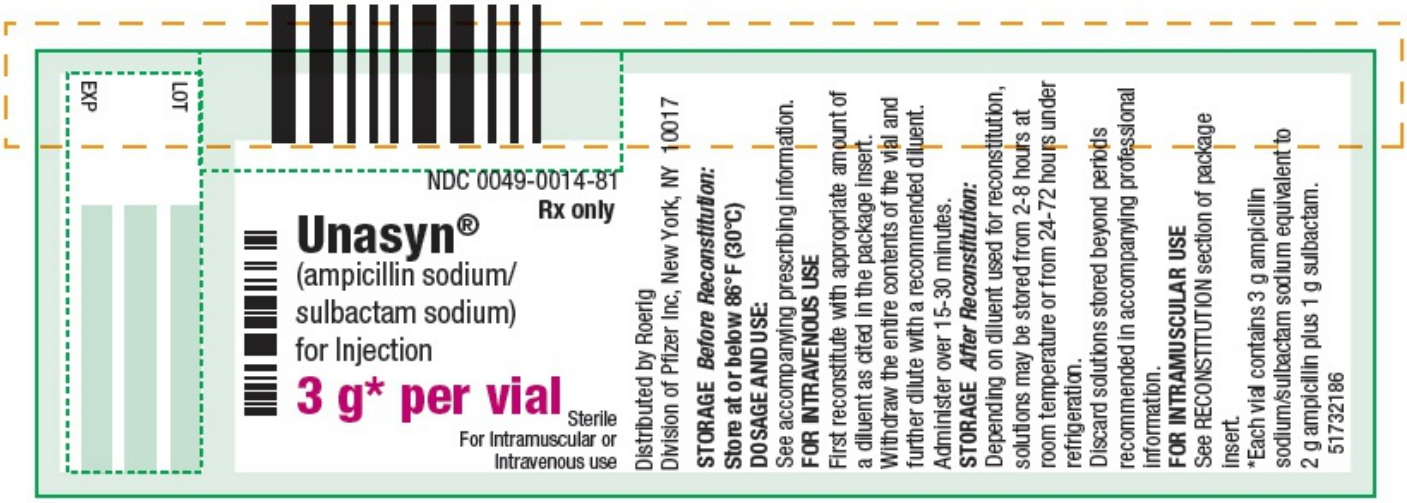
PRINCIPAL DISPLAY PANEL - 3 g Vial Label

NDC 0049-0014-81
Rx only

Unasyn®
(ampicillin sodium/
sulbactam sodium)
for Injection

3 g* per vial

Sterile
For Intramuscular or
Intravenous use



PRINCIPAL DISPLAY PANEL - 10 x 3 g Vial Carton

NDC 0049-0014-83
contains 10 of NDC 0049-0014-81
Rx only

10 Vials

Unasyn®
(ampicillin sodium/sulbactam sodium)
for Injection

3 g* per vial

Sterile

For Intramuscular or Intravenous use

Pfizer Injectables

S20X10K-INC

10 Vials

NDC 0049-0014-83
contains 10 of NDC 0049-0014-81
Rx only

Unasyn®

(ampicillin sodium/sulbactam sodium)
for Injection

3 g* per vial

Sterile
For Intramuscular or Intravenous use

Pfizer Injectables

10 Vials

Unasyn®

(ampicillin sodium/
sulbactam sodium)
for Injection

3 g* per vial

Sterile

For Intramuscular or Intravenous use

3IMIVIFC
51734991

10 Vials

Unasyn®

(ampicillin sodium/sulbactam sodium)
for Injection

3 g* per vial

Sterile
For Intramuscular or Intravenous use

Pfizer Injectables

STORAGE
Before Reconstitution:
Store at or below 86°F (30°C)

DOSAGE AND USE:
See accompanying prescribing information.
* Each vial contains 3 g ampicillin sodium/sulbactam sodium equivalent to 2 g ampicillin plus 1 g sulbactam.

MADE IN SPAIN

Distributed by
Roerig
Division of Pfizer Inc
New York, NY 10017

N 3 0049-0014-83 0

GTIN: 00300490014830
Lot
EXP

10 Vials

Unasyn®

(ampicillin sodium/
sulbactam sodium)
for Injection

3 g* per vial

Sterile

For Intramuscular or Intravenous use

PRINCIPAL DISPLAY PANEL - 3 g ADD-Vantage Vial Label

Single Dose
ADD-Vantage® Vial

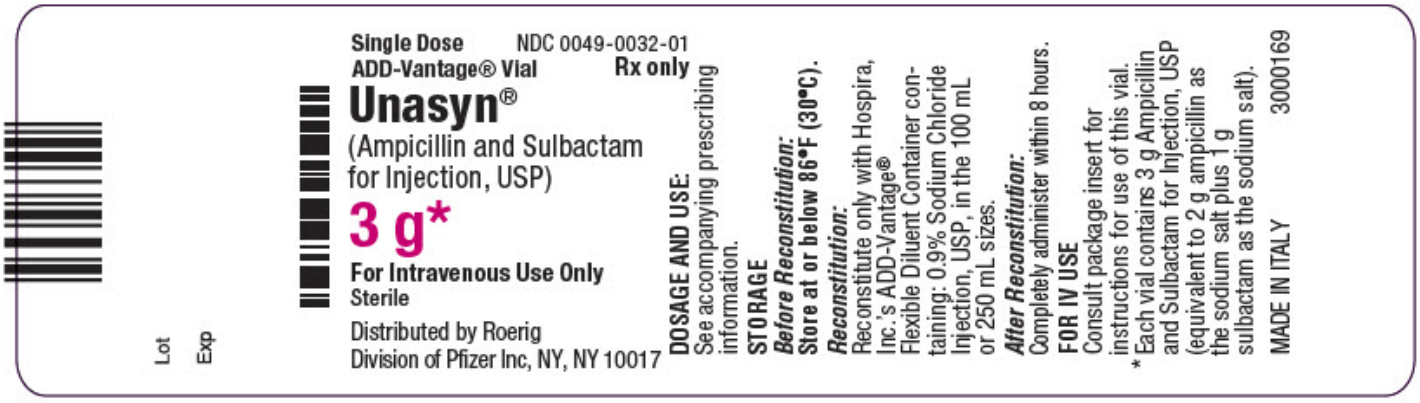
NDC 0049-0032-01
Rx only

Unasyn®
(Ampicillin and Sulbactam
for Injection, USP)

3 g*

For Intravenous Use Only
Sterile

Distributed by Roerig
Division of Pfizer Inc, NY, NY 10017



PRINCIPAL DISPLAY PANEL - 3 g ADD-Vantage Vial Carton

5 Single Dose
ADD-Vantage® Vials

NDC 0049-0032-02
Contains 5 of NDC 0049-0032-01

Unasyn®

3 g*

(Ampicillin and Sulbactam for Injection, USP)

For IV Use
Sterile

Pfizer Injectables

Rx only

5 Single Dose
ADD-Vantage® Vials

Unasyn®

3 g*

(Ampicillin and Sulbactam for Injection, USP)
For IV Use
Sterile

Pfizer Injectables

MADE IN ITALY
Distributed by
Roerig
Division of Pfizer Inc
NY, NY 10017

ADD-Vantage is a registered trademark of Hospira, Inc.

GTIN: 00300490032025
LOT: NBN NNN N
EXP: YYYY MMM DD
SN: NNN NNN NNN NNN

STORAGE
Before Reconstitution:
Store at or below 86°F (30°C).
After Reconstitution:
Completely administer as follows: In 0.9% Sodium Chloride Injection, USP-within 8 hours.
DOSAGE AND USE:
See accompanying prescribing information.
*Each 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).

N 0049-0032-02 5

5 Single Dose
ADD-Vantage® Vials

NDC 0049-0032-02
Contains 5 of NDC 0049-0032-01

Unasyn®

3 g*

(Ampicillin and Sulbactam for Injection, USP)
For IV Use
Sterile

Pfizer Injectables

Rx only

PRINCIPAL DISPLAY PANEL - 1.5 g ADD-Vantage Vial Label

Single Dose
ADD-Vantage® Vial

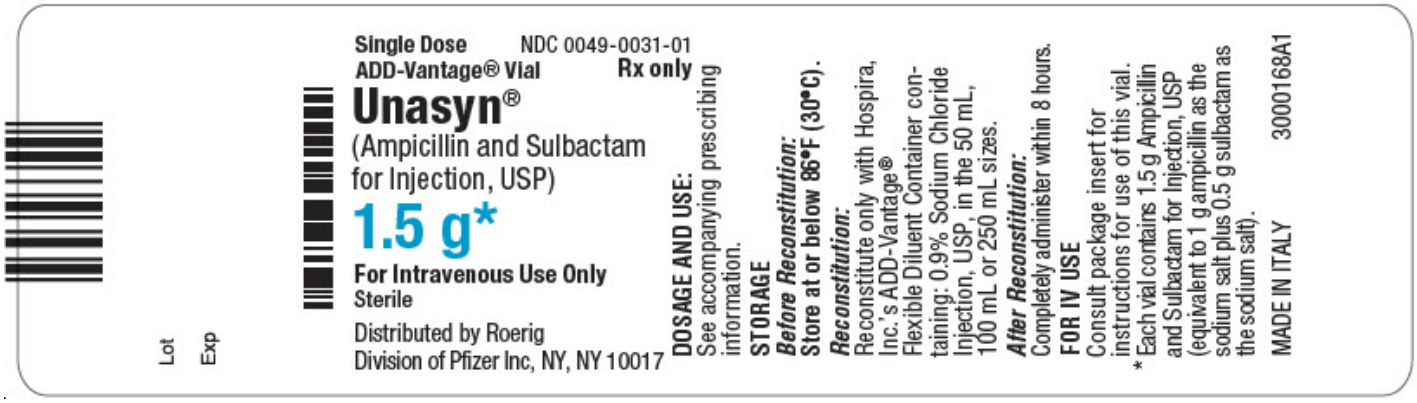
NDC 0049-0031-01
Rx only

Unasyn®
(Ampicillin and Sulbactam
for Injection, USP)

1.5 g*

For Intravenous Use Only
Sterile

Distributed by Roerig
Division of Pfizer Inc, NY, NY 10017



PRINCIPAL DISPLAY PANEL - 1.5 g ADD-Vantage Vial Carton

5 Single Dose
ADD-Vantage® Vials

NDC 0049-0031-02
Contains 5 of NDC 0049-0031-01

Unasyn®

1.5 g*

(Ampicillin and Sulbactam for Injection, USP)

For IV Use
Sterile

Pfizer Injectables

Rx only

5 Single Dose
ADD-Vantage® Vials

Unasyn®

1.5 g*

(Ampicillin and Sulbactam for Injection, USP)
For IV Use
Sterile

Pfizer Injectables

MADE IN ITALY

Distributed by
Roerig
Division of Pfizer Inc
NY, NY 10017

ADD-Vantage is a registered trademark of Hospira, Inc.

GTIN: 00300490031028

LOT: NB NNNNN
EXP: YYYY MMM DD
SN: NN NNNNNNNNN NN

STORAGE
Before Reconstitution:
Store at or below 86°F (30°C).
After Reconstitution:
Completely administer as follows: in 0.9% Sodium Chloride Injection, USP-within 8 hours.
DOSAGE AND USE:
See accompanying prescribing information.
*Each 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).

N 0049-0031-02 3

5 Single Dose
ADD-Vantage® Vials

NDC 0049-0031-02
Contains 5 of NDC 0049-0031-01

Unasyn®

1.5 g*

(Ampicillin and Sulbactam for Injection, USP)
For IV Use
Sterile

Pfizer Injectables

Rx only

UNASYN

ampicillin sodium and sulbactam sodium injection, powder, for solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0049-0013
Route of Administration	INTRAMUSCULAR, INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AMPICILLIN SODIUM (UNII: JFN36L5S8K) (AMPICILLIN - UNII:7C782967RD)	AMPICILLIN	1 g
SULBACTAM SODIUM (UNII: DKQ4T82YE6) (SULBACTAM - UNII:S4TF6I2330)	SULBACTAM	0.5 g

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0049-0013-83	10 in 1 CARTON	11/22/1991	
1	NDC:0049-0013-81	1 in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA050608	11/22/1991	

UNASYN

ampicillin sodium and sulbactam sodium injection, powder, for solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0049-0014
Route of Administration	INTRAMUSCULAR, INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AMPICILLIN SODIUM (UNII: JFN36L5S8K) (AMPICILLIN - UNII:7C782967RD)	AMPICILLIN	2 g
SULBACTAM SODIUM (UNII: DKQ4T82YE6) (SULBACTAM - UNII:S4TF6I2330)	SULBACTAM	1 g

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0049-0014-83	10 in 1 CARTON	11/22/1991	
1	NDC:0049-0014-81	1 in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA050608	11/22/1991	

UNASYN

ampicillin sodium and sulbactam sodium injection, powder, for solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0049-0032
Route of Administration	INTRAMUSCULAR, INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AMPICILLIN SODIUM (UNII: JFN36L5S8K) (AMPICILLIN - UNII:7C782967RD)	AMPICILLIN	2 g
SULBACTAM SODIUM (UNII: DKQ4T82YE6) (SULBACTAM - UNII:S4TF6I2330)	SULBACTAM	1 g

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0049-0032-02	5 in 1 CARTON	03/25/2019	03/25/2019
1	NDC:0049-0032-01	1 in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA062901	03/25/2019	03/25/2019

UNASYN

ampicillin sodium and sulbactam sodium injection, powder, for solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0049-0031
Route of Administration	INTRAMUSCULAR, INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AMPICILLIN SODIUM (UNII: JFN36L5S8K) (AMPICILLIN - UNII:7C782967RD)	AMPICILLIN	1 g
SULBACTAM SODIUM (UNII: DKQ4T82YE6) (SULBACTAM - UNII:S4TF6I2330)	SULBACTAM	0.5 g

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0049-0031-02	5 in 1 CARTON	03/25/2019	03/25/2019
1	NDC:0049-0031-01	1 in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA062901	03/25/2019	03/25/2019

Labeler - Roerig (829076996)

Establishment

Name	Address	ID/FEI	Business Operations
Haupt Pharma Latina Srl		338690598	ANALYSIS(0049-0013, 0049-0014) , MANUFACTURE(0049-0013, 0049-0014) , PACK(0049-0013, 0049-0014)

Establishment

Name	Address	ID/FEI	Business Operations
Pharmacia & Upjohn Company LLC		618054084	ANALYSIS(0049-0013, 0049-0014)