UNASYN

Ampicillin sodium and Sulbactam sodium

250 mg + 500 mg powder for injectable solution
500 mg + 1 g powder for injectable solution

Reference Market: US

AfME Markets using same as LPD: Saudi Arabia

SUMMARY OF PRODUCT CHARACTERISTICS

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.

1. NAME OF THE MEDICINAL PRODUCT

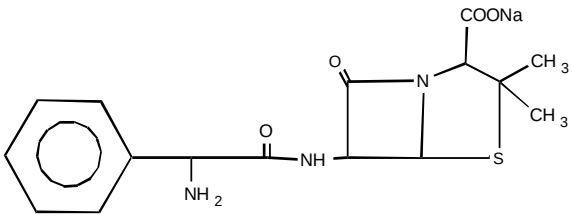
UNASYN 250 mg + 500 mg powder for injectable solution
UNASYN 500 mg + 1 g powder for injectable solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

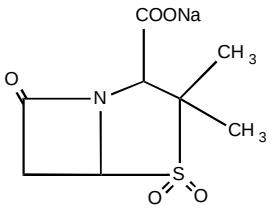
Each 0.75 g vial contains ampicillin 0.5 g and sulbactam 0.25 g (equivalent to 531.5 g ampicillin sodium and 273.5 g sulbactam sodium).
Each 1.5 g vial contains ampicillin 1 g and sulbactam 0.5 g (equivalent to 1.063 g ampicillin sodium and 0.547 g sulbactam sodium).

UNASYN (ampicillin and sulbactam) for Injection is a sterile antibacterial fixed combination drug product 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:



<u>Excipient with known effect:</u>
UNASYN contains Sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for injectable solution

UNASYN 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 colourless to pale yellow. The pH of dilute solutions remains the same.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 sections 4.4 and 5.1**)**.

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 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.

4.2 Posology and method of 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 mL–100 mL of a compatible diluent as an intravenous infusion over 15–30 minutes. (see section 6.6).

UNASYN may be administered by deep intramuscular injection. (see section 6.6).

The recommended adult dosage of UNASYN is 1.5 g (ampicillin 1 g and sulbactam 0.5 g) to 3 g (ampicillin 2 g and sulbactam 1 g) every six hours. This 1.5 g 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 and 0.5 g sulbactam to 2 g ampicillin and 1 g sulbactam. The total dose of sulbactam should not exceed 4 g 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 and 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 g per day. The course of intravenous therapy should not routinely exceed 14 days. In clinical trials, most pediatric patients received a course of oral antimicrobials following initial treatment with intravenous UNASYN. (see section 5.1).

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 1

UNASYN Dosage Guide for Patients with Renal Impairment

Creatinine Clearance (mL/min/1.73m^2)	Ampicillin and Sulbactam Half-Life (Hours)	Recommended UNASYN Dosage
≥30	1	1.5 g to 3 g every 6 to 8
15–29	5	1.5 g to 3 g every 12
5–14	9	1.5 g to 3 g every 24

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

4.3 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.

4.4 Special warnings and precautions for use

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), drug reaction with eosinophilia and systemic symptoms (DRESS), 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 sections 4.3 and 4.8).

Clostridioides difficile-Associated Diarrhea
Clostridioides 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 antibacterials 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 antibacterials which usually ends when the antibacterial is discontinued. Sometimes after starting treatment with antibacterials, 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.

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 sections 5.2, 4.1, 4.8, 4.2, and 5.1**)**.

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

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Fertility, pregnancy and lactation

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 section 4.4).

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.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

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.

Post-marketing Experience
In addition to adverse reactions reported from clinical trials, the following have been identified during post-marketing use of ampicillin sodium and 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 and sulbactam sodium.

Infections and Infestations: *Clostridioides difficile*- associated diarrhea (see section 4.4).

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, and black "hairy" tongue. (see sections 4.3 and 4.4).

General Disorders and Administration Site Conditions: Injection site reaction

Immune System Disorders: Serious and fatal hypersensitivity (anaphylactic) reactions (See 4.4), Acute myocardial ischemia with or without myocardial infarction may occur as part of an allergic reaction.

Metabolism and Nutrition Disorders: Hypokalemia

Nervous System Disorders: Convulsion and dizziness

Renal and Urinary Disorders: Tubulointerstitial nephritis

Musculoskeletal and Connective Tissue Disorders: Arthralgia

Respiratory, Thoracic and Mediastinal Disorders: Dyspnea

Skin and Subcutaneous Tissue Disorders: Toxic epidermal necrolysis, Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), angioedema, Acute generalized exanthematous pustulosis (AGEP), erythema multiforme, exfoliative dermatitis, and urticaria (see sections 4.3 and 4.4) and linear IgA bullous dermatosis.

Reporting of adverse reactions
Reporting suspected adverse reactions after marketing authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions according to their local requirements.

- **Saudi Arabia**

National Pharmacovigilance Centre (NPC)
- SFDA Call center : 19999
- E-mail: npc.drug@sfda.gov.sa
- Website: https://ade.sfda.gov.sa/

- **Other GCC States**

- *Please contact the relevant competent authority.*

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antibacterial agents for systemic use.
Penicillin combinations, including beta-lactamase inhibitors.
ATC code: J01CR01

MICROBIOLOGY

Mechanism of Action

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.

Antimicrobial Activity

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 Posology and method of administration 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)
Enterococcus faecalis†
Streptococcus pneumoniae†
Streptococcus pyogenes†
Streptococcus viridans†

Gram-negative Bacteria:
Hemophilus influenzae (beta-lactamase and non-beta-lactamase producing)
Moraxella 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
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

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.

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.

5.2 Pharmacokinetic properties

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 section 4.2).

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 3
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.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

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.

6.3 Shelf life

Do not use UNASYN after the expiry date which is stated on the vial label after EXP:. The expiry date refers to the last day of that month.

Shelf life: 24 months.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Clear, colorless Type III glass vials with bromobutyl rubber stoppers, aluminum caps, and colored flip-off over-caps.

The following packages are available:
Carton of 1 vial containing 0.75 mg (ampicillin 0.5 g and sulbactam 0.25 g)
Carton of 1 vial containing 1.5 g (ampicillin 1 g and sulbactam 0.5 g)

6.6 Special precautions for disposal and other handling

Keep out of the sight and reach of children.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

DIRECTIONS FOR USE:

General Dissolution Procedures:
UNASYN sterile powder for intravenous and intramuscular use may be reconstituted with any of the compatible diluents described for reconstitution 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 Standard Vial:

a) Reconstitute the vial with Sterile Water for Injection:

TABLE 4

UNASYN Vial Size	Volume of Sterile Water for Injection for Reconstitution
1.5 g	3.2 mL

- The reconstituted UNASYN solutions will have a total concentration of 375 mg/mL (ampicillin concentration of 250 mg/mL and sulbactam concentration of 125 mg/mL).
  The resultant volume post reconstitution for the 1.5 g vials is approximately 4 mL.

b) For intravenous infusion, immediately dilute with a suitable parenteral diluent (see Table 5) to yield solutions containing a total concentration between 3 mg/mL to 45 mg/mL of UNASYN (ampicillin concentration of 2 mg/mL to 30 mg/mL and sulbactam concentration of 1 mg/mL to 15 mg/mL).

Storage of Diluted UNASYN Solutions
Following dilution of reconstituted UNASYN, at the specified concentrations, the diluted solutions may be stored in the infusion bags based on conditions outlined in Table 5. After the indicated time periods, discard any unused portions of solutions.

TABLE 5

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

Preparation for Intramuscular Injection

1.5 g Standard Vial: Reconstitute the vials with Sterile Water for Injection USP, 0.5% Lidocaine Hydrochloride Injection USP or 2% Lidocaine Hydrochloride Injection USP. Consult Table 6 for recommended volumes to be added to obtain solutions containing a total UNASYN concentration of 375 mg/mL (ampicillin concentration 250 mg/mL and sulbactam concentration 125 mg/mL).

Note: *Use only freshly prepared solutions and administer within one hour after preparation.*

TABLE 6

UNASYN Vial Size	Volume of Diluent to be Added	Withdrawal Volume*
1.5 g	3.2 mL	4 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 sodium and sulbactam sodium therapy in man.

7. FURTHER INFORMATION

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8. DATE FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01-May-1993

9. DATE OF REVISION OF THE TEXT

November 2025