SULTAMICILLIN

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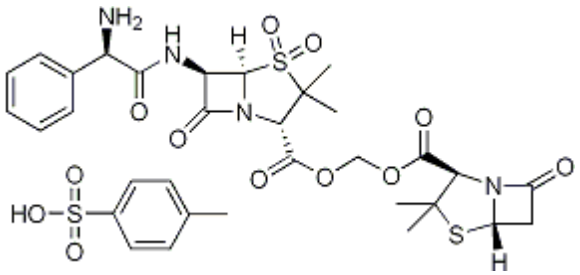
UNASYN®
250 mg/5 mL Powder for Oral Suspension
375 mg Tablet
750 mg Tablet

1.0 PHARMACOLOGIC CATEGORY

Antibacterial

2.0 DESCRIPTION

Sultamicillin is a double ester in which ampicillin and the beta-lactamase inhibitor sulbactam are linked via a methylene group. Chemically, sultamicillin is the oxymethylpenicillinate sulfone ester of ampicillin and has a molecular weight of 594.7.



3.0 FORMULATION/ COMPOSITION

Sultamicillin tosylate (Unasyn) 375 mg Film-Coated Tablet: Each tablet contains 375 mg sultamicillin (as tosylate) which is a mutual prodrug of sulbactam and ampicillin, yielding the equivalent of 147 mg sulbactam and 220 mg ampicillin.

Sultamicillin tosylate (Unasyn) 750 mg Film-Coated Tablet: Each tablet contains 750 mg sultamicillin (as tosylate) yielding the equivalent of 294 mg sulbactam and 440 mg ampicillin.

Sultamicillin (Unasyn) 60 mL Powder for Oral Suspension: Per 5 mL contains 250 mg sultamicillin.

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Sultamicillin is indicated for infections caused by susceptible microorganisms. Typical indications are upper respiratory tract infections including sinusitis, otitis media and tonsillitis; lower respiratory tract infections including bacterial pneumonias and

bronchitis; urinary tract infections and pyelonephritis; skin and soft tissue infections; intra-abdominal infections and gonococcal infections.

Sultamicillin may also be indicated in patients requiring sulbactam/ampicillin therapy following initial treatment with sulbactam/ampicillin IM/IV.

4.2 Dosage and Method of Administration

The recommended dose of sultamicillin in adults (including elderly patients) is 375-750 mg orally twice daily.

In both adults and children, treatment is usually continued until 48 hours after pyrexia and other abnormal signs have resolved. Treatment is normally given for 5-14 days but the treatment period may be extended if necessary.

In the treatment of uncomplicated gonorrhea, sultamicillin can be given as a single oral dose of 2.25 g (six 375 mg tablets or three 750 mg tablets). Concomitant probenecid 1.0 g should be administered in order to prolong plasma concentrations of sulbactam and ampicillin.

Cases of gonorrhea with a suspected lesion of syphilis should have dark field examinations before receiving sultamicillin and monthly serological tests for a minimum of four months.

It is recommended that there be at least 10 days treatment for any infection caused by hemolytic streptococci to prevent the occurrence of acute rheumatic fever or glomerulonephritis.

Use in Children and Infants

The dosage for most infections in children weighing less than 30 kg is sultamicillin 25-50 mg/kg/day orally in two divided doses, depending on the severity of the infection and the physician's judgment. For children weighing 30 kg or more, the usual adult dose should be given.

Use in Patients with Renal Impairment

In patients with severe impairment of renal function (creatinine clearance ≤30 mL/min), the elimination kinetics of sulbactam and ampicillin are similarly affected and hence the plasma ratio of one to the other will remain constant. The dose of sultamicillin in such patients should be administered less frequently in accordance with usual practice for ampicillin.

4.3 Contraindications

The use of sultamicillin is contraindicated in individuals with a history of an allergic reaction to any of the penicillins.

4.4 Special Warnings and Precautions for Use

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy including sultamicillin. 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 penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the appropriate therapy instituted.

Serious anaphylactic reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids, and airway management, including intubation, should be administered as indicated.

Severe skin reactions, such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), dermatitis exfoliative, and erythema multiforme have been reported in patients on ampicillin/sulbactam therapy. If a severe skin reaction occurs, use of the product should be discontinued and appropriate therapy should be initiated (see **Section 4.8 - Undesirable Effects**). As with any antibiotic preparation, constant observation for signs of overgrowth of non-susceptible organisms, including fungi, is essential. Should super-infection occur, the drug should be discontinued and/or appropriate therapy instituted.

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including sultamicillin, 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 antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Drug induced liver injury such as cholestatic hepatitis and jaundice have been associated with the use of ampicillin/sulbactam. Patients should be advised to contact their doctor if signs and symptoms of hepatic disease develop (see **Section 4.8 - Undesirable Effects**).

Since infectious mononucleosis is viral in origin, ampicillin should not be used in the treatment. A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash.

It is advisable to check periodically for organ system dysfunction during prolonged therapy; this includes renal, hepatic and hematopoietic systems.

The principal route of excretion of sulbactam and ampicillin following oral administration of sultamicillin is via the urine. Because renal function is not fully developed in neonates, this should be considered when using sultamicillin in neonates.

Tablets

Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Powder for Oral Suspension

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Allopurinol

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.

Anticoagulants

Penicillins can produce alterations in platelet aggregation and coagulation tests. These effects may be additive with anticoagulants.

Bacteriostatic drugs (chloramphenicol, erythromycin, sulfonamides and tetracyclines)

Bacteriostatic drugs may interfere with the bactericidal effect of penicillins; it is best to avoid concurrent therapy.

Estrogen-containing oral contraceptives

There have been case reports of reduced oral contraceptive effectiveness in women taking ampicillin, resulting in unplanned pregnancy. Although the association is weak, patients should be given the option to use an alternate or additional method of contraception while taking ampicillin.

Methotrexate

Concurrent use with penicillins has resulted in decreased clearance of methotrexate and a corresponding increase in methotrexate toxicity. Patients should be closely monitored. Leucovorin dosages may need to be increased and administered for longer periods of time.

Probenecid

Probenecid decreases renal tubular secretion of ampicillin and sulbactam when used concurrently; this effect results in increased and prolonged serum concentrations, prolonged elimination half-life, and increased risk of toxicity.

Laboratory test interactions

False-positive glycosuria may be observed in urinalysis using Benedict reagent, Fehling reagent, and Clinitest™. 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 sulbactam sodium/ampicillin sodium IM/IV.

4.6 Fertility, Pregnancy and Lactation

Use During Pregnancy

Animal reproduction studies have revealed no evidence of impaired fertility or harm to the fetus due to sultamicillin. Sulbactam and ampicillin cross the placental barrier. However, safety for use in human pregnancy has not been established. Therefore, sultamicillin should be used during pregnancy only if the potential benefits outweigh the potential risk.

Use During Lactation

The use of sultamicillin during lactation is not recommended. Low concentrations of ampicillin and sulbactam are excreted in the milk. This should be considered as the neonate may be exposed, particularly since renal function is not fully developed in neonates.

4.7 Effects on Ability to Drive and Use Machines

None known

4.8 Undesirable Effects

Sultamicillin is generally well tolerated. The majority of side effects observed were of mild or moderate severity and were normally tolerated with continued treatment.

Infections and Infestations: Pseudomembranous colitis, Candida infection.

Blood and Lymphatic System Disorders: Thrombocytopenia.

Immune System Disorders: Anaphylactic shock, Anaphylactic reaction, Kounis syndrome, Hypersensitivity.

Nervous System Disorders: Dizziness, Somnolence, Sedation, Headache.

Respiratory, Thoracic and Mediastinal Disorders: Dyspnea.

Gastrointestinal Disorders: Enterocolitis, Melena, Diarrhea, Vomiting, Abdominal pain, Dyspepsia, Nausea, Stomatitis, Dysgeusia, Tongue discoloration.

Hepatobiliary Disorders: Jaundice, Hepatic function abnormal (see **Section 4.4 - Special Warnings and Precautions for Use**).

Skin and Subcutaneous Tissue Disorders: Toxic epidermal necrolysis, Stevens-Johnson syndrome, Erythema multiforme (see **Section 4.4 - Special Warnings and Precautions for Use**), Angioedema, Urticaria, Dermatitis, Rash, Pruritus.

Musculoskeletal and Connective Tissue Disorders: Arthralgia.

General Disorders and Administration Site Conditions: Fatigue, Malaise.

Investigations: Alanine aminotransferase increased, Aspartate aminotransferase increased (see **Section 4.4 - Special Warnings and Precautions for Use**).

Adverse reactions associated with the use of ampicillin alone and/or sulbactam/ampicillin IM/IV may be observed with sultamicillin. These include:

Blood and Lymphatic System Disorders: Agranulocytosis, Hemolytic anemia, Thrombocytopenic purpura, Leukopenia, Neutropenia, Eosinophilia, Anemia.

Immune System Disorders: Anaphylactoid shock, Anaphylactoid reaction.

Nervous System Disorders: Convulsion.

Gastrointestinal Disorders: Glossitis.

Hepatobiliary Disorders: Hepatitis cholestatic, Cholestasis, Hyperbilirubinemia (see **Section 4.4 - Special Warnings and Precautions for Use**).

Skin and Subcutaneous Tissue Disorders: Dermatitis exfoliative, Acute generalized exanthematous pustulosis (see **Section 4.4 - Special Warnings and Precautions for Use**).

Renal and Urinary Disorders: Tubulointerstitial nephritis.

Investigations: Platelet aggregation abnormal.

4.9 Overdose and Treatment

Limited information is available on the acute toxicity of ampicillin sodium and sulbactam sodium in humans. Overdosage of the drug would be expected to produce manifestations that are principally extensions of the adverse reactions reported with the drug. The fact that high cerebrospinal fluid (CSF) concentrations of beta-lactam antibiotics may cause neurologic effects, including seizures, should be considered. Because ampicillin and sulbactam are both removed from the circulation by hemodialysis, these procedures may enhance elimination of the drug from the body if overdosage occurs in patients with impaired renal function.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Biochemical studies with cell-free bacterial systems have shown sulbactam to be an irreversible inhibitor of most important beta-lactamases that occur in penicillin-resistant organisms. While sulbactam antibacterial activity is mainly limited to *Neisseriaceae*, the potential for sulbactam sodium in preventing the destruction of penicillins and cephalosporins by resistant organisms was confirmed in whole-organism studies using resistant strains, in which sulbactam sodium exhibited marked synergistic effects with penicillins and cephalosporins. Since sulbactam also binds to some penicillin-binding proteins, some sensitive strains are rendered more susceptible to the combination than to the beta-lactam antibiotic alone.

The bactericidal component of this product is ampicillin, which, like benzyl penicillin, acts against sensitive organisms during the stage of active multiplication by the inhibition of biosynthesis of cell wall mucopeptide.

Sultamicillin is effective against a wide range of gram-positive and gram-negative bacteria including: *Staphylococcus aureus* and *Staphylococcus epidermidis* (including penicillin-resistant and some methicillin-resistant strains); *Streptococcus pneumoniae*, *Streptococcus faecalis* and other *Streptococcus* species; *Haemophilus influenzae* and *Haemophilus parainfluenzae* (both beta-lactamase-positive and -negative strains); *Moraxella catarrhalis*; anaerobes including *Bacteroides fragilis* and related species; *Escherichia coli*; *Klebsiella* species; *Proteus* species (both indole-positive and indole-negative); *Enterobacter* species; *Morganella morganii*; *Citrobacter* species; *Neisseria meningitidis* and *Neisseria gonorrhoeae*.

5.2 Pharmacokinetic Properties

Following oral administration in humans, sultamicillin is hydrolyzed during absorption to provide sulbactam and ampicillin in a 1:1 molar ratio in the systemic circulation. The bioavailability of an oral dose is 80% of an equal intravenous dose of sulbactam and

ampicillin. Administration following food does not affect the systemic bioavailability of sultamicillin. Peak serum levels of ampicillin, following administration of sultamicillin, are approximately twice those of an equal dose of oral ampicillin. Elimination half-lives are approximately 0.75 and 1 hour for sulbactam and ampicillin, respectively, in healthy volunteers, with 50%-75% of each agent being excreted unchanged in the urine. Elimination half-lives are increased in the elderly and in patients with renal dysfunction. Probenecid decreases the renal tubular secretion of both ampicillin and sulbactam. Concurrent use of probenecid with sultamicillin results in increased and prolonged blood levels of ampicillin and sulbactam (see **Section 4.5 - Interaction with Other Medicinal Products and Other Forms of Interaction**).

5.3 Preclinical Safety Data

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 humans.

Long-term studies in animals have not been performed to evaluate the carcinogenic potential. The individual components of sultamicillin (ampicillin/sulbactam) tested negative for mutagenicity.

Reproduction studies have been performed in mice and rats at doses in excess of the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to sultamicillin.

6.0 PHARMACEUTICAL PARTICULARS

6.1 Directions for Reconstitution for Sultamicillin Powder for Oral Suspension

Ingest only after preparation of a suspension. The bottle with the powder for oral suspension should be filled with water up to the marking line. It should then be shaken until the content is uniformly mixed; then subsequently fill again with water up to the same marking line and shake again. The suspension now can be used for 14 days if stored in the refrigerator. Shake before each use.

6.2 Shelf-Life

Please see outer packaging for shelf-life data.

6.3 Storage Condition

375 mg Tablet: Store at temperatures not exceeding 30°C.

250 mg/5 mL Powder for Oral Suspension and 750 mg Tablet: Store at temperatures not exceeding 25°C.

The reconstituted oral suspension must be stored under refrigeration and discarded after 14 days.

6.4 Availability

375 mg Tablet: White, capsular-shaped film-coated tablets available in box of 100's.

750 mg Tablet: A white to off-white, capsular-shaped film-coated tablets available in box of 8's.

250 mg/5 mL Powder for Oral Suspension: White to off-white powder for reconstitution in 60 mL bottle.

6.5 Special Precautions for Disposal and Other Handling

Not applicable

7.0 FDA REGISTRATION NUMBER

375 mg Tablet: DRP-3451
750 mg Tablet: DRP-2076
250 mg/5 mL Powder for Oral Suspension: DRP-2015

8.0 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

375 mg Tablet: 01 July 1989
750 mg Tablet: 02 September 2003
250 mg/5 mL Powder for Oral Suspension: 09 August 1990

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Manufactured by:

375 mg Tablet:
Pfizer Global Supply Japan, Inc.
Aza 5-gochi, Taketoyo-Cho
Chita-Gun, Aichi-Ken, Nagoya, Japan

750 mg Tablet and 250 mg/5 mL Powder for Oral Suspension:
Haupt Pharma Latina S.r.l.

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04100 Borgo San Michele, Latina, Italy

Marketing Authorization Holder:
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Under the authority of Pfizer Inc., New York, New York, U.S.A.

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