PFIZER

UNASYN*

(sultamicillin tosylate)
For Oral Use

1. NAME OF THE MEDICINAL PRODUCT

UNASYN TAB 375 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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 sulphone ester of ampicillin and has a molecular weight of 594.7.

3. PHARMACEUTICAL FORM

Sultamicillin is available as film-coated tablets containing the tosylate salt equivalent to 375 mg sultamicillin, which is a mutual prodrug of sulbactam and ampicillin, yielding the equivalent of 147 mg sulbactam and 220 mg ampicillin.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Sultamicillin is indicated for infections caused by susceptible micro-organisms. 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 and gonococcal infections.

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

4.2. Posology 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). 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 judgement. 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 reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with sultamicillin (sulbactam sodium/ampicillin sodium), careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, sultamicillin (sulbactam sodium/ampicillin sodium) must be discontinued immediately and appropriate alternative 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), drug reaction with eosinophilia and systemic symptoms (DRESS), dermatitis exfoliative, erythema multiforme, and acute generalized exanthematous pustulosis (AGEP) have been reported in patients

on ampicillin/sulbactam therapy. If a severe skin reaction occurs, ampicillin/sulbactam 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 superinfection 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.

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

4.5. Interaction with Other Medicinal Products and Other Forms of Interaction

<u>Allopurinol</u>
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.

<u>Anticoagulants</u>

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.

ADRs associated with sultamicillin by SOC and CIOMS frequency category listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC

System Organ Class	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Frequency not known (cannot be estimated from the available data)**
Infections and Infestations	Candida infection			Pseudomembranous colitis
Blood and lymphatic system disorders				Thrombocytopenia
Immune system disorders				Anaphylactic shock, Anaphylactic reaction, Kounis syndrome, Hypersensitivity
Nervous system disorders	Headache	Dizziness		Somnolence, Sedation
Respiratory, thoracic and mediastinal disorders				Dyspnea
Gastrointestinal disorders	Diarrhea, Vomiting, Abdominal pain, Nausea	Melena, Stomatitis		Enterocolitis, Dyspepsia, Dysgeusia, Tongue discoloration
Hepatobiliary disorders				Jaundice, Hepatic function abnormal
Skin and subcutaneous tissue disorders	Rash, Pruritus	Dermatitis		Toxic epidermal necrolysis, Stevens-Johnson syndrome, Drug reaction with eosinophilia and systemic symptoms, Erythema multiforme, Angioedema, Urticaria

Musculoskeletal and connective tissue disorders		Arthralgia		
General disorders and administration site conditions		Fatigue, Malaise		
Investigations				Alanine aminotransferase increased, Aspartate aminotransferase increased

ADRs associated with ampicillin alone and/or sulbactam/ampicillin IM/IV by SOC and CIOMS frequency category listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC

System Organ Class	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Frequency not known (cannot be estimated from the available data)**
Blood and lymphatic system disorders				Agranulocytosis, Hemolytic anemia, Thrombocytopenic purpura, Leukopenia, Neutropenia, Eosinophilia, Anemia
Immune system disorders				Anaphylactoid shock, Anaphylactoid reaction
Metabolism and nutrition disorders				Hypokalemia
Nervous system disorders				Convulsion
Gastrointestinal disorders		Glossitis		
Hepatobiliary disorders				Hepatitis cholestatic, Cholestasis, Hyperbilirubinemia
Skin and subcutaneous tissue disorders				Dermatitis exfoliative, Acute generalized exanthematous pustulosis, Linear IgA disease
Renal and urinary disorders				Tubulointerstitial nephritis
Investigations				Platelet aggregation abnormal

4.9. Overdose

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. 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. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Lactose, Corn Starch, Sodium Starch Glycolate, Hydroxypropylcellulose, Magnesium Stearate, Hydroxypropylmethylcellulose 2910, Titanium Oxide, Talc, Macrogol 6000, Purified water, Carnauba Wax, and specially denatured alcohol.

6.2. Incompatibility

None known.

6.3. Shelf-life

Please refer to carton for expiry date.

6.4. Special Precautions for Storage

Please refer to carton for storage condition.

6.5. Nature and Contents of Container

375 mg tablets are available in packs of 100's.

6.6. Instructions for Use/Handling

Keep out of the reach of children.

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