

## **SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

UNASYN

## 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 sulfone ester of ampicillin and has a molecular weight of 594.7.

### UNASYN 375 mg film-coated tablets

Each film-coated tablet contains:

Active principle: Sultamicillin tosylate 520.80 mg, equal to sultamicillin 375 mg  
Sultamicillin 375 mg equal to 147 mg sulbactam and 220 mg ampicillin

### UNASYN 750 mg Tablets

Each tablet contains:

Active principle: Sultamicillin tosylate 1012.60 mg, equal to sultamicillin 750 mg  
Sultamicillin 750 mg are equal to 294 mg sulbactam and 440 mg ampicillin

### UNASYN 250 mg powder for oral suspension

One bottle of powder contains:

Active principle: Sultamicillin 5 g  
Sultamicillin 5 g are equal to 1.96 g sulbactam and 2.93 g ampicillin

After dilution with water, 5 ml suspension contains:

Active principle: Sultamicillin 250 mg.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Sultamicillin is available as uncoated tablets and 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.

Sultamicillin is also available as a powder for oral suspension containing sultamicillin base that, after reconstitution with water, provides 250 mg sultamicillin per 5 ml.

## 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 gonorrhoea, 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 gonorrhoea 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  $\leq 30$  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 nonsusceptible 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.

#### 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.<sup>21</sup>

### **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 crosses 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

Immune System Disorders: Anaphylactic shock, Anaphylactic reaction, Hypersensitivity<sup>3</sup>

Nervous System Disorders: Dizziness, Somnolence, Sedation, Headache

Respiratory, Thoracic and Mediastinal Disorders: Dyspnoea

Gastrointestinal Disorders: Enterocolitis, Melaena, Diarrhoea, Vomiting, Abdominal pain, Dyspepsia, Nausea

Skin and Subcutaneous Tissue Disorders: Angio-oedema, Urticaria, Dermatitis, Rash, Pruritus

General Disorders and Administration Site Conditions: Fatigue, Malaise

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

Blood and Lymphatic System Disorders: Agranulocytosis, Haemolytic anaemia, Thrombocytopenic purpura, Thrombocytopenia, Leukopenia, Neutropenia, Eosinophilia, Anaemia

Nervous System Disorders: Convulsion<sup>4</sup>

Gastrointestinal Disorders: Glossitis, Stomatitis, Tongue discolouration<sup>4</sup>

Hepatobiliary Disorders: Hepatitis cholestatic, Cholestasis, Hyperbilirubinaemia, Hepatic function abnormal, Jaundice (see Section 4.4 - Special warnings and precautions for use).

Skin and Subcutaneous Tissue Disorders: Toxic epidermal necrolysis, Stevens-Johnson syndrome, Erythema multiforme, Dermatitis exfoliative (see Section 4.4 - Special warnings and precautions for use).

Renal and Urinary Disorders: Tubulointerstitial nephritis

Investigations: Platelet aggregation abnormal, Alanine aminotransferase increased, Aspartate aminotransferase increased.

#### **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. There are, however, no adequate and well-controlled studies in pregnant women.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

#### UNASYN 375 mg film-coated tablets

**Lactose anhydrous**, dried cornstarch, sodium glycolate starch, hydroxypropylcellulose, stearate magnesium.

*Overcoat*: macrogol 6000, hypromellose, titanium dioxide (E171), talc.

#### UNASYN 750 mg film-coated tablets

**Lactose anhydrous**, dried cornstarch, sodium glycolate starch, hydroxypropylcellulose, stearate magnesium.

*Overcoat*: macrogol 6000, hypromellose, titanium dioxide (E171), talc.

UNASYN 250 mg powder for oral suspension:

**Sucrose**, colloidal silica, bibasic sodium phosphate anhydrous, monobasic sodium phosphate anhydrous, cherry fragrance.

## **6.2. Incompatibilities**

Not applicable.

## **6.3. Shelf life**

**Keep out of the sight and reach of children.**

**Do not use UNASYN after the expiry date which is stated on the carton / Blister / Bottle after EXP:. The expiry date refers to the last day of that month.**

**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.**

## **6.4. Special precautions for storage**

Instructions for Use/Handling

Powder for Oral Suspension: Shake well before use.

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

Film Coated Tablets and Powder for Oral Suspension: Keep out of the reach of children.

## **6.5. Nature and contents of container**

UNASYN 375 mg film-coated tablets: Blister containing 12 tablets.

UNASYN 750 mg film-coated tablets: Blister containing 8 tablets.

UNASYN 250 mg powder for oral suspension: High density polyethylene 100 ml bottle containing 5 g of sultamicillin.

Not all formulations and pack sizes may be registered.

## **6.6. Special precautions for disposal and other handling**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.



### Reconstitution instructions 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.

## **7. FURTHER INFORMATION**

### **MANUFACTURED BY**

Haupt Pharma Latina S.R.L  
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04100 Borgo S. Michele  
Latina - Italy January 2012

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## **9. DATE OF REVISION OF THE TEXT**

October 2016