Sultamicillin Tosilate

Ampimax®

750 mg Film-Coated Tablet

ANTIBACTERIAL (Penicillin/Beta-Lactamase Inhibitor)

FORMULATION

Each film-coated tablet contains:
Sultamicillin (as tosilate dihydrate) .....750 mg
(Equivalent to Ampicillin 440 mg and Sulbactam 294 mg)

PRODUCT DESCRIPTION

Sultamicillin is a prodrug of ampicillin and of the beta-lactamase inhibitor sulbactam. It consists of the two compounds linked as a double ester.

Sultamicillin (Ampimax®) 750 mg is a white to almost white oblong shaped biconvex film-coated tablet with one side engraved with "CF" and the other side notched.

PHARMACODYNAMICS

Ampicillin is an aminopenicillin which exerts its bactericidal activity by interfering with the synthesis of the bacterial cell wall. It inhibits transpeptidase, an enzyme responsible for the synthesis of the peptidoglycan layer of the bacterial cell wall. This results in the interruption of peptidoglycan synthesis causing spheroplast formation and bacterial lysis.

Sulbactam is a penicillanic acid sulfone with beta-lactamase inhibitory properties. It is an irreversible inhibitor of many plasmid-mediated and some chromosomal beta-lactamases and has a similar spectrum of beta-lactamase inhibition as clavulanic acid. Sulbactam can therefore enhance the activity of penicillins and cephalosporins against many strains of bacteria.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

Sultamicillin has demonstrated bactericidal activity against the following microorganisms:

Aerobic Gram-positive	Aerobic Gram-negative
Staphylococcus aureus (including penicillin-resistant and some methicillin-resistant strains) *Staphylococcus epidermidis* (including penicillin-resistant and some methicillin-resistant strains) *Streptococcus pneumoniae* *Streptococcus faecalis* Other *Streptococcus* spp.	*Haemophilus influenzae* (both beta-lactamase positive and negative strains) *Haemophilus parainfluenzae* (both beta-lactamase positive and negative strains) *Moraxella catarrhalis* *Escherichia coli* *Klebsiella* spp. *Proteus* spp. (both indole-positive and indole-negative) *Enterobacter* spp. *Morganella morganii* *Citrobacter* spp. *Neisseria meningitidis* *Neisseria gonorrhoeae*
Anaerobes	
Bacteroides fragilis and related species	

PHARMACOKINETICS

After oral administration, sultamicillin is hydrolyzed during absorption to equivalent molar quantities (1:1) of ampicillin and sulbactam. The bioavailability of an oral dose of sultamicillin is 80% of an equal intravenous (IV) dose of ampicillin and sulbactam.

Food does not affect the systemic bioavailability of sultamicillin. After sultamicillin administration, peak serum levels of ampicillin are approximately twice those of an equal dose of oral ampicillin. Elimination half-lives are about 1 hour and 0.75 hour for ampicillin and sulbactam, respectively, in healthy volunteers, with 50-75% of each drug being excreted unchanged in the urine. The elimination half-lives are increased in the elderly and in patients with renal impairment. Probenecid decreases the renal tubular secretion of both ampicillin and sulbactam.

INDICATIONS

- For the treatment of the following infections caused by susceptible microorganisms:
  - Upper respiratory tract infections including sinusitis, otitis media, epiglottitis, and tonsillitis
  - Lower respiratory tract infections including bacterial pneumonia and bronchitis
  - Urinary tract infections including pyelonephritis
  - Intraabdominal infections including peritonitis, cholecystitis, endometritis, and pelvic cellulitis
  - Bacterial septicemia
  - Skin and skin structure infections
  - Bone and joint infections
  - Gonococcal infections
- As step down treatment for infections due to susceptible organisms, initially given antimicrobial therapy, particularly parenteral ampicillin-sulbactam.

DOSAGE AND ADMINISTRATION

Usual Dose in Adults and Children weighing ≥ 30 kg who can swallow tablet whole: 750 mg twice daily

Usual Duration of Treatment: 5 to 14 days which may be extended depending on the type and severity of infection.

Non-complicated gonococcal infection: 2.25 g (three 750 mg tablets) as a single dose

- For most infections, therapy should be continued for a minimum of 48 hours after the patient becomes asymptomatic or evidence of bacterial eradication has been obtained.
- In the treatment of group A ß-hemolytic streptococcal infections, penicillin therapy should be continued for at least 10 days to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.
- 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.

Or, as prescribed by a physician.

CONTRAINDICATIONS

- Known hypersensitivity to penicillins, sulbactam or any component of the product.
- Patients with infectious mononucleosis since they have an increased tendency to develop maculopapular rash while taking ampicillin.

WARNINGS and PRECAUTIONS

- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy including sultamicillin. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or hypersensitivity to multiple allergens. Careful inquiry should be made concerning previous hypersensitivity to penicillins, cephalosporins or other drugs before initiating therapy with sultamicillin. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy instituted.

  Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, IV steroids, and airway management, including intubation, should be administered as indicated.

- *Clostridium difficile*-associated diarrhea (CDAD) and colitis have been reported with the use of nearly all antibacterial agents, including sultamicillin, and may range in severity from mild to life threatening. It is important to consider this diagnosis in patients who present with diarrhea following administration of antibacterial agents.
- The renal, hepatic, and hematologic status of patients undergoing prolonged treatment with aminopenicillins should be evaluated periodically, particularly when administered to patients with liver or renal impairment.
- Prescribing sultamicillin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of antibiotic resistance.
- As with other antibacterial agents, long term or repeated use may result in overgrowth of non-susceptible organisms, including fungi.

INTERACTIONS WITH OTHER MEDICAMENTS

- **Allopurinol:** An increased incidence of rash reportedly occurs in patients with hyperuricemia who are receiving allopurinol and concomitant ampicillin compared with those receiving ampicillin or allopurinol alone.
- **Aminoglycosides:** Both ampicillin and sulbactam are potentially physically and/or chemically incompatible with aminoglycosides and can inactivate the drugs *in vitro.*
- **Anticoagulants:** Alterations in platelet aggregation and coagulation tests have been reported with penicillin use. Increased anticoagulant activity may also be expected.
- **Bacteriostatic Drugs (e.g., erythromycin, sulfonamides and tetracyclines):** These drugs may interfere with the bactericidal effect of penicillins; therefore, concurrent therapy is not recommended.
- **Chloramphenicol:** *In vitro* evidence of antagonism with ampicillin has been observed.
- **Chloroquine:** The absorption of ampicillin has been reduced in patients taking chloroquine.
- **Methotrexate:** Concomitant use of penicillins may result in decreased renal clearance of methotrexate and subsequent increase in methotrexate toxicity.
- **Estrogen-containing Oral Contraceptives:** Possible decreased efficacy of estrogen-containing oral contraceptives and increased incidence of breakthrough bleeding have been reported with ampicillin.
- **Probenecid:** Oral probenecid administered shortly before or concomitantly with ampicillin and sulbactam competitively inhibits renal tubular secretion of both ampicillin and sulbactam and produces higher and prolonged serum concentrations of the drugs.
- **Others:** Variable *in vitro* effects from additive or indifferent to antagonistic effects have been demonstrated when ampicillin is used in conjunction with rifampicin or acetohydroxamic acid.

Interference with Laboratory Tests:

Ampicillin reportedly interferes with urinary glucose determinations using cupric sulfate (e.g., Benedict's solution, Clinitest®) but does not affect glucose oxidase methods (Clinistix®, Tes-Tape®).

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy: Reproduction studies of sultamicillin in animals have revealed no evidence of impaired fertility or harm to fetus. Although ampicillin alone has been administered to pregnant women without evidence of adverse effect to the fetus, the safety of sultamicillin use during pregnancy has not been definitely established.

Lactation: Use with caution in breastfeeding women. Low concentrations of ampicillin and sulbactam are excreted in human milk. This should be considered as the neonate may be exposed, particularly since renal function is not fully developed in neonates.

Elderly: Although serum half-lives of ampicillin and sulbactam are slightly longer in elderly patients than in younger adults, dosage of sultamicillin does not need to be modified in elderly patients with normal renal function. However, since these patients have increased risk of renal impairment, renal function monitoring may be necessary.

Renal Impairment: In patients with severe renal impairment (creatinine clearance ≤30 mL/min), the elimination kinetics of ampicillin and sulbactam 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.

UNDESIRABLE EFFECTS

Sultamicillin is generally well-tolerated. Most adverse effects (AEs) are mild to moderate in severity and are normally tolerated with continued treatment.

Body as a Whole: Fatigue/malaise and headache have been rarely observed

Dermatologic / Hypersensitivity reactions: Rash, itching, pemphigus vulgaris, angioedema, dermatitis, urticaria; allergic reaction, anaphylaxis/anaphylactic shock, anaphylactoid reaction, superinfections, adult respiratory distress syndrome

Gastrointestinal (GI): Vomiting, nausea, diarrhea, loose stools, epigastric distress, melena, abdominal pain/cramps

Nervous system: Taste disturbances, ototoxicity, dizziness, drowsiness/sedation

Renal: Kidney function disorder

Respiratory: Dyspnea

The following AEs have also been reported for aminopenicillin-class antibiotics including ampicillin and/or parenteral ampicillin/sulbactam:

Dermatologic/Hypersensitivity reactions: Pruritus, dry skin, erythema; rare reports of exfoliative dermatitis, toxic epidermal necrolysis, erythema multiforme, and Stevens-Johnson syndrome; serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever); systemic allergic reactions (characterized by neck tightness, difficulty and pain when breathing, generalized weakness, and hypertension); facial swelling; positive direct antiglobulin (Coombs' test)

GI: Anorexia, gastritis, black hairy tongue, glossitis, stomatitis, CDAD and colitis; acute, transient enterocolitis with severe abdominal pain and bloody diarrhea, but without evidence of CDAD and colitis; acute pancreatitis; flatulence, abdominal discomfort or distension, rectal bleeding

Nervous system: Headache, confusion; rare reports of convulsions/myoclonic seizures; generalized seizures

Hematologic: Anemia, hemolytic anemia, hypothrombinemia, eosinophilia, leukopenia, neutropenia, agranulocytosis, thrombocytopenia, thrombocytopenic purpura, abnormal platelet aggregation, prolongation of bleeding time, and prolongation of activated partial thromboplastin time (APTT); decreased hemoglobin concentration, hematocrit, erythrocyte, lymphocyte, and platelet counts; increased lymphocyte, monocyte, basophil, eosinophil, and platelet counts

Hepatobiliary: Transient elevations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, lactate dehydrogenase (LDH), creatine kinase (CK), bilirubin, and γ-glutamyltransferase (γ-glutamyltranspeptidase, GT, GGTP); bilirubinemia, abnormal hepatic function, and jaundice

Renal: Rare reports of acute interstitial nephritis; glomerulonephritis; increased blood urea nitrogen (BUN) and serum creatinine concentrations; presence of red blood cells and hyaline casts in urine, urine retention, dysuria, hematuria, crystalluria

Other Adverse Effects: Decreased concentrations of serum albumin and total protein; chest pain or tightness, edema, chills, throat tightness, substernal pain, epistaxis, mucosal bleeding; changes in smell perception

OVERDOSE AND TREATMENT

Ampicillin + sulbactam overdose may manifest as extensions of the drugs' adverse effects. It should be considered that high CSF concentrations of beta-lactam antibiotics may cause neurologic effects including seizures.

Since ampicillin and sulbactam are removed by hemodialysis, this procedure should be considered during overdosage in patients with renal impairment. For overdosage in patients with normal renal function, hemodialysis may not be necessary and only appropriate measures should be taken.

STORAGE CONDITIONS

Store at temperatures not exceeding 25°C.
Keep the product out of sight and reach of children.

AVAILABILITY

Sultamicillin Tosilate (Ampimax®) 750 mg tablet in Alu/Alu blister pack by 5's (box of 10's)

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

ADVERSE DRUG REACTION REPORTING STATEMENT

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

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