Alphacin

Ampicillin (trihydrate)

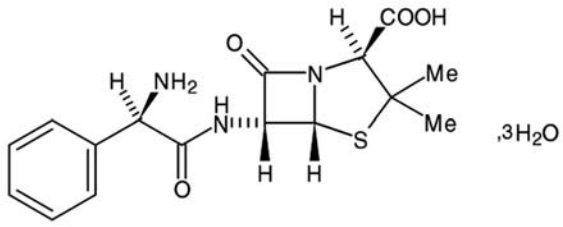
PRODUCT INFORMATION

NAME OF THE MEDICINE

Active ingredient: Ampicillin trihydrate

Chemical name: (2*S*,5*R*,6*R*)-6-[[(2*R*)-2-amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid

Structural formula:



Molecular formula: $C_{16}H_{19}N_3O_4S,3H_2O$ Molecular weight: 403.5

CAS Registry No.: 7177-48-2

DESCRIPTION

Ampicillin is a broad spectrum semisynthetic penicillin.

It is a white crystalline powder which is odourless or almost odourless with a bitter taste. It is soluble in 150 parts of water and is almost insoluble in ethanol (96%), in chloroform, in solvent ether, and in fixed oils.

Each Alphacin 250 and Alphacin 500 capsule contains 250 mg and 500 mg of ampicllin (trihydrate) as the active ingredient respectively. Each capsule contains the following inactive ingredients: talc – purified, sodium starch glycollate, magnesium stearate, sodium lauryl sulfate, gelatin, silica – colloidal anhydrous, titanium dioxide, erythrosine CI45430, iron oxide yellow CI77492. Alphacin 250 capsules also contain cellulose – microcrystalline.

PHARMACOLOGY

Microbiology

Ampicillin is bactericidal and is active against a wider range of organisms than benzylpenicillin. Like benzylpenicillin, ampicillin is bactericidal to sensitive organisms during the stage of active cell division. It is believed to act through the inhibition of cell wall synthesis.

Gram-positive

It is less active against Gram-positive organisms but is active *in vitro* against *Streptococcus pyogenes* (Group A, beta-haemolytic Streptococci) and many strains of *Streptococcus pneumoniae* (*D. pneumoniae*), *Streptococcus viridans,* non-penicillinase producing Staphylococci and *Enterococcus faecalis* (Group D Streptococci and except *Enterococcal endocarditis*).

Gram-negative
There are strains of *Escherichia coli* that are sensitive to ampicillin, but isolates are becoming increasingly resistant *in vitro* due to the presence of penicillinase-producing strains. Some of the above organisms are sensitive to ampicillin only at concentrations achieved in the urine. Many strains of *Haemophilus influenzae, Neisseria meningitidis, Proteus mirabilis* and Salmonella are sensitive to ampicillin, although the increasing incidence of beta-lactamase activity in *H. influenzae* and *E. coli* are reducing the capacity of ampicillin to treat diseases caused by these organisms.

Resistance
Resistance to ampicillin occurs as a result of inactivation by beta-lactamase (penicillinase) hydrolysis. Ampicillin is not effective against penicillinase-producing bacteria, particularly resistant Streptococci, which are now common. All strains of Pseudomonas, indole-positive Proteus, *Serratia marcescens*, Enterobacter, Klebsiella, Citrobacter and penicillinase producing *N. gonorrhoeae* are resistant.

Susceptibility Tests

Dilution or diffusion techniques, either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (eg. NCCLS). Standardised susceptibility test procedures require the use of laboratory control micro-organisms to control the technique aspects of the laboratory procedures.

A report of 'susceptible' indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations achievable.

A report of 'intermediate' indicates that the result should be considered equivocal, and if the micro-organism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation.

A report of 'resistant' indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note. The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Pharmacokinetics

Therapeutic Drug Concentration. Ampicillin produces high and persistent blood levels. A dose-response relationship has been demonstrated in fasting adults following oral administration of ampicillin. 1 to 2 hours after administration of 250 mg, 500 mg and 1 g, serum concentrations achieved were 1.3 to 3.5 mcg/mL, 2.8 to 4.9 mcg/mL and 4.5 to 8.5 mcg/mL respectively.

Time to Peak Concentration. Oral, 1 to 2 hours.

Absorption. Approximately 30 to 54% of dose. Diarrhoea has variable effect on absorption. Absorption from peritoneal cavity produces serum concentrations in renal failure patients comparable to an IM dose in healthy individuals.

Effects of Food. Absorption may be delayed and impaired in the presence of food.

Distribution. Protein binding: Ampicillin is not highly protein bound; 29 $\pm$ 12% is reported to be protein bound in the serum.

Ampicillin sodium diffuses readily into most body tissues and fluids with the exception of brain and spinal fluid. Some penetration occurs through inflamed meninges but maximum cerebrospinal fluid levels are very much lower than peak serum levels.

Volume of Distribution. 19.5 to 27 Litres.

Excretion. Following oral administration; approximately 30% is excreted unchanged in the urine within 6 hours of administration. Excretion of ampicillin can be delayed by concurrent administration of probenecid, thus prolonging its therapeutic effect.

Other Excretion. Bile, about 0.1%.

Elimination Half-Life. Approximately 1 hour with normal renal function and up to 20 hours in the total absence of renal function.

Ampicillin is excreted in the urine both unchanged and as penicilloic acid.

INDICATIONS

Indicated in the treatment of infections due to susceptible strains of Gram-positive and Gram-negative organisms (see **Microbiology**).

Bacteriological studies to determine the organisms and its sensitivity should be undertaken.

CONTRAINDICATIONS

Ampicillin is a penicillin and should not be given to patients with a history of a hypersensitivity to beta-lactam antibiotics (eg. penicillins, cephalosporins).

PRECAUTIONS

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients receiving beta-lactam antibiotics. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral therapy.

Before commencing therapy with any beta-lactam antibiotic, careful enquiries should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If a hypersensitivity reaction occurs, appropriate therapy should be instituted and ampicillin therapy discontinued. Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids, and airway management, including intubation should also be administered as indicated.

Pseudomembranous Colitis. Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including ampicillin. A toxin produced with *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases, appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, eg. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Caution should be exercised in the treatment of patients with an allergic diathesis.

Ampicillin is not the treatment of choice in patients presenting with sore throat or pharyngitis. This is because the underlying cause may be infectious mononucleosis, in the presence of which there is a high incidence of rash if ampicillin is used. Patients with lymphatic leukaemia also appear to have a higher incidence of skin rashes when treated with ampicillin.

As with any potent drug, periodic assessment of renal, hepatic and haemopoietic function should be made during prolonged therapy.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving Enterobacter, Pseudomonas, or Candida), the drug should be discontinued and/or appropriate therapy instituted.

Indwelling urethral catheters should be checked regularly as the high concentrations of ampicillin in the urine may cause it to precipitate out of solution at room temperature. The risk of crystalluria should be avoided by maintaining a high urinary output.

Use in Pregnancy (Category A)

Ampicillin diffuses across the placenta into the foetal circulation. Animal studies with ampicillin have shown no teratogenic effects. Ampicillin has been in clinical use for nearly 30 years and the limited number of reported cases of use in human pregnancy have shown no evidence of untoward effect. The use of ampicillin in pregnancy should be reserved for cases considered essential by the clinician.

Use in Labour and Delivery

Studies in guinea pigs have shown that intravenous administration of ampicillin decreases uterine tone and the frequency, strength and duration of contractions. However, it is not known whether the use of ampicillin in humans during labour or delivery has immediate or delayed adverse effects, prolongs the duration of labour or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn infant will be necessary.

Use in Lactation

Ampicillin is excreted in breast milk. An alternative feeding method is recommended to avoid any possible sensitisation in the infant.

Interactions with Other Medicines

Probenecid decreases the renal tubular secretion of ampicillin. Concurrent use with ampicillin may result in increased and prolonged blood levels of ampicillin.

Tetracyclines, erythromycin and chloramphenicol antagonise the action of ampicillin.

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 hyperuricaemia present in these patients.

In common with other antibiotics, patients should be warned that ampicillin may reduce the effectiveness of oral contraceptives.

Effects on Laboratory Tests

As administration of ampicillin will result in high ampicillin concentrations in the urine, false positive reactions may be elicited when testing the urine for glucose with Clinitest, Benedict's Solution or Fehling's Solution. Tests based on enzymatic glucose oxidase reactions such as Clinistix or Testape should be used instead.

Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated oestriol, oestriol-glucuronide, conjugated oestrone and oestradiol has been noted.

ADVERSE EFFECTS

As with all penicillins, the possibility of allergic reactions should always be considered. Reactions are more likely to occur in those with an allergic diathesis. Anaphylactic shock is most likely to occur with injected penicillins.

The following adverse reactions have been reported as associated with the use of ampicillin.

Gastrointestinal. Glossitis, stomatitis, black hairy tongue, nausea, vomiting, and diarrhoea. These reactions are usually associated with oral dosage forms.

Hypersensitivity Reactions. An erythematous maculopapular rash has been reported fairly frequently. A macular rash, which is not believed to be a hypersensitivity reaction, occurs predominantly in patients with infectious mononucleosis four to five days after beginning therapy with ampicillin.

Urticaria and erythema multiforme have been reported occasionally. A few cases of exfoliative dermatitis have been reported. Anaphylaxis is the most serious reaction experienced (see **Precautions**).

Note. Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to ampicillin therapy.

Hepatic. A moderate rise in aspartate aminotransferase (AST) has been noted, particularly in infants, but the significance of this finding is unknown. As with other beta-lactam antibiotics, hepatitis and cholestatic jaundice have been reported rarely.

Haematological. Anaemia, thrombocytopenia, haemolytic anaemia, thrombocytopenic purpura, eosinophilia, leucopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of the therapy and are believed to be sensitivity reactions.

Renal. Nephropathy has been reported rarely.

Central Nervous System. Encephalopathy can occur when the ampicillin blood level reaches 800 mg/L. As the blood brain barrier becomes more permeable in meningitis, toxic symptoms may be precipitated by lower levels of ampicillin in patients with meningitis. This can result in drowsiness, hyper-reflexia, myoclonic twitches, convulsions and coma.

Other. Vaginal or oral moniliasis may occur following the use of antibiotics.

72% of all adverse events to ampicillin recorded in the Australian Adverse Drug Reaction System include rash as a symptom.

DOSAGE AND ADMINISTRATION

Doses to be taken one hour before meals.

Respiratory Tract Infections.	Adults: 250 to 500 mg every six hours. Children: 25 to 50 mg/kg/day in equally divided doses every six hours.
Chronic Bronchitis.	Adults: 500 mg every six hours (high dosage therapy: 1 g six hourly).
Urinary Tract Infections.	Adults: 500 mg six hourly. Children: 50 mg/kg/day in equally divided doses every six hours.
Gastrointestinal Tract Infections.	Adults: 500 to 750 mg six hourly. Children: 50 to 70 mg/kg/day in equally divided doses, six hourly.

The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than recommended for adults. Children weighing more than 20 kg should be dosed according to the adult recommendation.

It should be recognised that frequent bacteriological and clinical appraisals are necessary in the treatment of chronic urinary tract and intestinal infections.

Smaller doses than those recommended above should not be used. Higher doses may be needed at times. The usual duration of therapy is 5 to 10 days, but in some cases therapy may be required for longer durations. Treatment should be continued for a minimum of 48to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days treatment for any infection caused by haemolytic streptococci to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

Patients with Impaired Renal Function. In renal impairment, the excretion of the antibiotic will be delayed and, depending on the degree of impairment, it may be necessary to reduce the total daily dosage. The following regime has been suggested:

Glomerular Filtration Rate (mL/min)	Dose	Dosage Interval (hr)
10 to 50	Normal	6 to 12
< 10	Normal	12 to 16

OVERDOSAGE

Encephalopathy can occur when the ampicillin blood level reaches 800 mg/L. As the blood brain barrier becomes more permeable in meningitis, toxic symptoms may be precipitated by lower levels of ampicillin in patients with meningitis. This can result in drowsiness, hyper-reflexia, myoclonic twitches, convulsions and coma.

There is no specific treatment for ampicillin overdosage. Ampicillin is removed by haemodialysis. Patients usually recover as the penicillin blood level decreases.

PRESENTATION AND STORAGE CONDITIONS

Alphacin 250, 250 mg capsule: green body with red cap; bottle 24's.

Alphacin 500, 500 mg capsule: green body with red cap; bottle 24's.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF APPROVAL

Approved by the Therapeutic Goods Administration on 14 December 2004.