

PRODUCT INFORMATION
AMOXYCILLIN SANDOZ®
250/500mg CAPSULE, 125/250mg/5mL SUSPENSIONS

NAME OF THE MEDICINE

Active Ingredient: Amoxicillin trihydrate

Inactive Ingredients:

Capsules:

Magnesium stearate, microcrystalline, gelatin, iron oxide yellow and titanium dioxide.

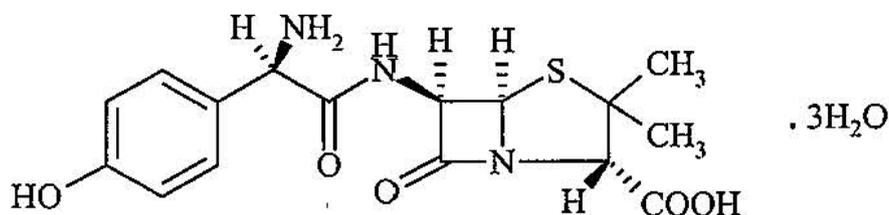
Powder for Oral Suspension:

Anhydrous citric acid, sodium benzoate, aspartame, purified talc, sodium citrate anhydrous, guar gum, silicon dioxide, lemon flavouring, peach-apricot flavouring and orange flavouring.

DESCRIPTION

Amoxicillin trihydrate is a white or almost white, crystalline powder. It is slightly soluble in water and in ethanol (96%); practically insoluble in chloroform, in ether and in fatty oils.

Structural Formula:



Chemical Name: (2*S*, 5*R*, 6*R*)-6-[(*R*)-2-amino-2-(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.

Molecular Formula: $\text{C}_{16} \text{H}_{19} \text{N}_3 \text{O}_5 \text{S} \cdot 3\text{H}_2\text{O}$

Molecular Weight: 419.4

CAS Number: 61336-70-7

PHARMACOLOGY

Microbiology

Amoxicillin trihydrate is a broad-spectrum penicillin similar to ampicillin in its bactericidal action. It is believed to act through the inhibition of biosynthesis of cell wall mucopeptide. It is active against both gram-positive and gram-negative microorganisms. Amoxicillin is

active *in vitro* against beta-lactamase negative strains of *Proteus mirabilis*, and *Haemophilus influenzae*. *In vitro* studies have also demonstrated activity against most strains of alpha- and beta-haemolytic streptococci. *Streptococcus pneumoniae*, and beta-lactamase negative strains of staphylococci, *Neisseria gonorrhoeae*, *Neisseria meningitidis* and *Enterococcus faecalis*. However, some of the organisms are sensitive to amoxicillin only at concentrations achieved in the urine. Strains of gonococci which are relatively resistant to benzyl penicillin may also be resistant to amoxicillin. Amoxicillin is not effective against penicillinase producing bacteria, particularly resistant staphylococci which now have a high prevalence. All strains of *Pseudomonas*, *Klebsiella*, *Enterobacter*, indole positive *Proteus*, *Serratia marcescens*, *Citrobacter*, penicillinase producing *N. gonorrhoeae* and penicillinase producing *H. influenzae* are also resistant. *Escherichia coli* isolates are becoming increasingly resistant to amoxicillin *in vitro* due to the presence of penicillinase-producing strains.

Acquired resistance for amoxicillin in Australia*

ORGANISM	% RESISTANT STRAINS
<i>S. pneumoniae</i>	16.8% intermediate resistance; 8.6% resistant
<i>H. influenzae</i>	20.3%
<i>M. catarrhalis</i>	94.0%
<i>B. fragilis</i>	100%
<i>Enterobacter spp.</i>	96%
<i>Klebsiella spp</i>	98%
<i>P. aeruginosa</i>	100%
<i>S. aureus (methicillin-susceptible)</i>	85%
<i>Enterococcus faecalis</i>	0.2%
<i>Enterococcus faecium</i>	80%
<i>E. coli</i>	45.4%
<i>P. mirabilis</i>	14%

*Therapeutic Guidelines Antibiotic 2000 Edition

Disc Susceptibility Testing

Dilution of 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 microorganisms to control the technical 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 usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism 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 may 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

Amoxicillin is stable in the presence of gastric acid and is rapidly and well absorbed after oral administration, even in the presence of food. Peak serum levels are reached within one or two hours after ingestion. Amoxicillin readily distributes in most body tissues and fluids with the exception of brain and spinal fluid except when the meninges are inflamed. Amoxicillin has been shown to diffuse into sputum and saliva and is excreted mainly via the urine where it exists in a high concentration. Concentrations in the bile may vary and are dependent upon normal biliary function. Amoxicillin is eliminated with a half-life of 61.3 minutes with normal renal function and up to 16-20 hours in the absence of renal function. Amoxicillin is excreted in the urine as unchanged drug and as penicilloic acid. Approximately 75% of a 1g dose is excreted in the urine within six hours with normal renal function. However, there is a proportional difference in the amount excreted following different doses, due to lack of linearity in the rate of absorption with higher doses. Elimination of amoxicillin can be delayed by concurrent administration of probenecid. Amoxicillin is only 17% protein bound in serum.

Orally administered doses of amoxicillin 250 and 500 mg result in average peak serum levels one to two hours after administration of 5 microgram/mL and 10.25 microgram/mL respectively. Detectable serum levels of amoxicillin are present eight hours after ingestion of a single dose.

INDICATIONS

Treatment of the following infections due to susceptible strains of sensitive organisms:

Note:

Therapy should be guided by bacteriological studies, including sensitivity tests, and by clinical response. Amoxicillin alone or in combination with another antibiotic, may be used in an emergency where the causative has not been identified.

- Respiratory tract infections (acute and chronic): *H. influenzae*; Streptococcus; *S. pneumoniae*; Staphylococcus, nonpenicillinase producing; *E. coli* (see Microbiology).
- Urogenital infections (complicated and uncomplicated, acute and chronic): *E. coli* (see Microbiology), *P. mirabilis* and *Strep. faecalis*.
- Gonorrhoea: *N. gonorrhoea* (nonpenicillinase producing).
- Skin and skin structure infections: Staphylococcus, nonpenicillinase producing; Streptococcus; *E. coli* (see Microbiology).
- Prophylaxis of endocarditis: Amoxicillin may be used for the prophylaxis of bacterial endocarditis in individuals at particular risk, such as those with a prosthetic heart valve or those who have previously had endocarditis.

Infections caused by pathogens with established penicillin G susceptibility should preferentially be treated with penicillin G.

CONTRAINDICATIONS

Amoxicillin is a penicillin and should not be given to patients with a history of hypersensitivity to β -lactam antibiotics (e.g. penicillins, cephalosporins, carbapenem or monobactam). Known and suspected hypersensitivity to penicillins. Potential cross allergy to other beta-lactams such as cephalosporins should be taken into account.

Known hypersensitivity to the active substance, to any of the penicillins or to any of the excipients.

Antibiotics have no place in trivial infections.

PRECAUTIONS

Serious, and occasionally fatal, hypersensitivity (anaphylactoid) reactions have been reported in patients receiving penicillin therapy. These reactions are more frequently associated with parenteral therapy but have been reported for patients receiving oral penicillins. Careful assessment should be made prior to administration of amoxicillin to determine any previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. Amoxicillin therapy should be immediately discontinued if hypersensitivity reactions occur. Patients should be told about the potential occurrence of allergic reactions and instructed to report them.

If allergic reactions occur, the drug should be discontinued and the usual treatment with adrenaline, antihistamines and corticosteroids should be instituted, as necessary.

Serious anaphylactoid reactions should be treated with adrenaline. Oxygen, intravenous steroids and airways management, including intubation should be administered as necessary.

Non-susceptible microorganisms: Amoxicillin is not suitable for the treatment of some types of infection unless the pathogen is already documented and known to be susceptible or there is a very high likelihood that the pathogen would be suitable for treatment with amoxicillin. This particularly applies when considering the treatment of patients with urinary tract infections and severe infections of the ear, nose and throat.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including amoxicillin. A toxin produced by *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). If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further. 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 conditions and should not be used.

Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving amoxicillin and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

As with any potent drug, periodic assessment of renal, hepatic and haematopoietic function should be made during prolonged therapy. The possibility of superinfection with mycotic or bacterial pathogens should be kept in mind. If superinfection occurs (usually involving *Aerobacter*, *Pseudomonas* or *Candida*) discontinue the drug and/or institute appropriate therapy.

Amoxicillin should be given with caution to patients with lymphatic leukaemia as they are susceptible to amoxicillin induced skin rashes.

Amoxicillin should not be used for the treatment of bacterial infections in patients with viral infections, presenting with sore throat, pharyngitis or infectious mononucleosis, as a high incidence of amoxicillin induced erythematous (morbilliform) rashes have been associated with glandular fever in patients receiving Amoxicillin.

Jarisch-Herxheimer reaction: The Jarisch-Herxheimer reaction has been seen following amoxicillin treatment of Lyme disease. It results directly from the bactericidal activity of amoxicillin on the causative bacteria of Lyme disease, the spirochaete *Borrelia burgdorferi*. Patients should be reassured that this is a common and usually self-limiting consequence of antibiotic treatment of Lyme disease

Special caution should be exercised in patients with allergic diatheses or bronchial asthma and hay fever.

Following single dose therapy of acute lower urinary tract infections, the urine should be cultured. A positive culture may be evidence of a complicated or upper urinary tract infection, and higher dose or prolonged course of treatment may be appropriate.

The presence of high urinary concentrations of Amoxicillin can cause precipitation of the product in urinary catheters. Therefore, catheters should be visually inspected at intervals. At high doses, adequate fluid intake and urinary output must be maintained to minimise the possibility of Amoxicillin crystalluria.

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. This effect may also occur with amoxicillin.

Precaution should be taken in premature children and during neonatal period: renal, hepatic and haematological functions should be monitored.

As with other beta-lactams, the blood formula should be checked regularly during high-dose therapy. Elevated liver enzymes and changes in blood counts have been reported.

High dose therapy with beta-lactams for patients with renal insufficiency or seizures history, treated epilepsy and meningeal affection, could exceptionally lead to seizures. Dosage

should be adjusted in patients with renal impairments (see DOSAGE AND ADMINISTRATION).

The occurrence of a generalized erythema with fever and pustules at the beginning of treatment should make suspect a generalized acute exanthematic pustulosis; this necessitates the interruption of therapy and contraindicated any further administration of Amoxycillin.

Fertility

There are no data on the effects of amoxycillin on fertility in humans. Reproductive studies in animals have shown no effects on fertility.

Use in Pregnancy

Category A:

Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

Animal studies with amoxycillin have shown no teratogenic effects. The product has been in extensive clinical use since 1972 and its suitability in human pregnancy has been well documented in clinical studies.

Amoxycillin may be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Use in Labour and Delivery

Oral ampicillin class antibiotics are generally poorly absorbed during labour. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions and duration of contractions. However, it is not known whether the use of amoxycillin in humans during labour or delivery has immediate or delayed adverse effects on the foetus, prolongs the duration of labour or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Use in Lactation

Ampicillin class antibiotics are excreted in breast milk and caution should be exercised when amoxycillin is administered to nursing mothers. So far no detrimental effects for the breast-fed infant have been reported after taking Amoxycillin. Amoxycillin can be used during breast-feeding. However, breast-feeding must be stopped if gastrointestinal disorders (diarrhoea, candidosis or skin rash) occur in the new born

Effects on laboratory tests

Oral administration of amoxycillin will result in high urine concentrations of amoxycillin. Since high urine concentrations of amoxycillin may result in false positive reactions when testing for the presence of glucose in urine using Clinistest, Benedict's Solution or Fehling's Solution, it is recommended that glucose tests based on enzyme-based glucose oxidase reactions (such as Clinistix, or Testape) be used

INTERACTIONS WITH OTHER MEDICINES

Allopurinol

Concomitant ingestion of allopurinol and ampicillin may promote the occurrence of skin rashes. The underlying mechanism is still poorly understood. Similar reactions can be expected with amoxicillin.

Digoxin

An increase in the absorption of digoxin is possible on concurrent administration with Amoxicillin. A dose adjustment of digoxin may be necessary.

Anticoagulants

Concomitant administration of Amoxicillin and anticoagulants from the coumarin class, may prolong the bleeding time. A dose adjustment of anticoagulants may be necessary (See Precautions). If coadministration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin.

A large number of cases showing an increase of oral anticoagulant activity has been reported in patients receiving antibiotics. The infectious and inflammatory context, age and the general status of the patient appear as risk factors. In these circumstances, it is difficult to know the part of the responsibility between the infectious disease and its treatment in the occurrence of INR disorders. However, some classes of antibiotics are more involved, notably fluoroquinolones, macrolides, cyclines, cotrimoxazole and some cephalosporins

Probenecid

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin.

Tetracyclines

Tetracyclines and other bacteriostatic drugs may interfere with the bactericidal effects of amoxicillin.

Methotrexate

Interaction between Amoxicillin and methotrexate leading to methotrexate toxicity has been reported. Serum methotrexate levels should be closely monitored in patients who receive Amoxicillin and methotrexate simultaneously (see Precautions). Amoxicillin decreases the renal clearance of methotrexate, probably by competition at the common tubular secretion system.

Caution is recommended when Amoxicillin is given concomitantly with:

Oral hormonal contraceptives

Administration of Amoxicillin can transiently decrease the plasma level of oestrogens and progesterone, and may reduce the efficacy of oral contraceptives. It is therefore recommended to take supplemental non-hormonal contraceptive measures.

Other forms of interactions:

- Forced diuresis leads to a reduction in blood concentrations by increased elimination of Amoxicillin
- Amoxicillin may decrease the amount of urinary estriol in pregnant women.

- At high concentrations, Amoxicillin may diminish the results of serum glycemia levels.
- Amoxicillin may interfere with protein testing when colormetric methods are used

ADVERSE EFFECTS

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins.

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and skin rash.

The following adverse reactions have been reported as associated with the use of amoxicillin:

Gastrointestinal. Nausea, vomiting, diarrhoea. Intestinal candidiasis, antibiotic associated colitis (including pseudomembranous colitis and haemorrhagic colitis), superficial discoloration of the teeth (especially with the suspension) have been reported rarely (see Precautions). Usually the discoloration can be removed by teeth brushing. If severe and persistent diarrhoea occurs, the very rare possibility of pseudomembranous colitis should be considered. The administration of anti-peristaltic drug is contraindicated. Black hairy tongue and haemorrhagic colitis have been reported very rarely.

Hypersensitivity. Erythematous maculopapular rash, pruritus and urticaria have been reported occasionally. Rarely, skin reactions such as erythema multiforme exsudativum, acute generalised pustulosis, Lyell's syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis and bullous and exfoliative dermatitis acute generalised exanthematous pustulosis (AGEP) and Jarisch-Herxheimer reaction have been reported. As with other antibiotics, severe allergic reactions including angioneurotic oedema, anaphylaxis, serum sickness, hypersensitivity vasculitis and interstitial nephritis (crystalluria) have been reported rarely. Whenever such reactions occur, amoxicillin should be discontinued.

Note. Urticaria, other skin rashes and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids.

Anaphylaxis is the most serious reaction experienced (see Precautions).

Hepatic. A moderate rise in AST and/or ALT has occasionally been noted, but the significance of this finding is unknown. As with other beta-lactam antibiotics, hepatitis and cholestatic jaundice have been reported rarely.

Haemic and lymphatic systems. Reactions such as anaemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia and leucopenia (including severe neutropenia or agranulocytosis) have been reported during therapy with other penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. Prolongation of bleeding time and prothrombin time have also been reported rarely.

Central nervous system effects. CNS effects have been seen rarely. They include hyperkinesia, dizziness and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Infections and infestations. Mucocutaneous candidiasis have been reported very rarely.

Renal and urinary tract disorders. Interstitial nephritis, crystalluria have been reported very rarely.

Miscellaneous. Superficial tooth discolouration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.

DOSAGE AND ADMINISTRATION

Normal renal function:

Upper respiratory tract infections; genitourinary tract infections; skin and soft tissue infections:

Adults: 250 mg every eight hours

Children (under 20 kg): 20 mg/kg/day in equally divided doses, every 8 hours

In severe infections or those caused by less susceptible organisms, 500 mg every eight hours for adults and 40 mg/kg/day in equally divided doses every 8 hours for children may be needed.

Lower respiratory tract infections:

Adults: 500 mg every eight hours

Children (under 20 kg): 40 mg/kg/day every 8 hours in equally divided doses

Urethritis, gonococcal:

Adults: 3 g as a single dose.

Cases of gonorrhoea with a suspected lesion of syphilis should have darkfield examinations before receiving amoxicillin and monthly serological tests for a minimum of 4 months.

Acute, uncomplicated lower urinary tract infections in non-pregnant adult females:

3 g as a single dose.

Use in neonates:

Experience in neonates is too limited to make any recommendations regarding dosage or the appropriateness of the oral route.

Use in children:

The children's dosage is intended for individuals whose weight will not cause dosage greater than that recommended for adults. Children receiving amoxicillin every 8 hours and weighing more than 20 kg should receive the adult recommended doses.

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 doses.

In patients receiving peritoneal dialysis, the maximum recommended dose is 500 mg/day. Amoxicillin may be removed from the circulation by haemodialysis.

Chronic urinary tract infections:

Frequent biological and clinical appraisals are recommended for patients under treatment for chronic urinary tract infections. Doses smaller than those recommended should not be used. Therapy for stubborn infections may have to be extended for several weeks.

Bacteriological and clinical appraisals may have to be continued for several months following cessation of treatment.

Duration of treatment:

Treatment should be continued for a minimum of 48 to 72 hours beyond the time when patients become asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be a minimum of 10 days treatment for any infection caused by haemolytic streptococci to prevent occurrence of acute rheumatic fever or glomerulonephritis.

Prophylaxis of endocarditis:

Dental Procedures. Prophylaxis for patients undergoing extraction, scaling or surgery involving gingival tissues, who are not having general anaesthetic, and who have not received a penicillin in the previous month. (*Note:* Patients with prosthetic heart valves should be referred to hospital.)

Adults (including elderly): 3 g orally, 1 hour before procedure. A second does may be given 6 hours later if considered necessary.

Children:

<i>Under 10 years:</i>	Half adult dose
<i>Under 5 years:</i>	Quarter adult dose

(*Note:* Prophylaxis with alternative antibiotics should be considered if the patient has received penicillin within the previous month, or is allergic to penicillin.)

OVERDOSAGE

Signs of overdosage of amoxicillin would predominately be gastrointestinal related. The symptoms may include abdominal or stomach cramps and pain, severe nausea, vomiting or diarrhoea. Treatment of penicillin overdosage should be symptomatic and supportive. Haemodialysis may aid in the removal of penicillins from the blood.

Please refer to Precautions and Adverse Reactions.

PRESENTATION AND STORAGE CONDITIONS

Amoxicillin Sandoz[®] Powder for Suspension is a white to slightly yellowish powder available in 60 mL & 100 mL bottles. It contains 125 mg/5 mL or 250 mg/5 mL amoxicillin (as trihydrate)

Amoxicillin Sandoz[®] Capsules are white to cream powder in an opaque yellow hard gelatin capsule available in a blister pack of 20 capsules. Each capsule contains 250 mg or 500 mg amoxicillin (as trihydrate).

Amoxicillin Sandoz[®] Capsules: Store below 25° C, protect from moisture.

Amoxicillin Sandoz[®] Powder for Oral Suspension:

Powder: Store below 25°C. Keep the container tightly closed.

After Mixing: Store in a refrigerator (2°C-8°C). Discard unused suspension after 14 days.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE: S4

DATE OF FIRST INCUSION ON THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 22nd May 2008

DATE OF MOST RECENT AMENDMENT: 11/04/2016