

# AMOXIL DUO™

## NAME OF THE DRUG

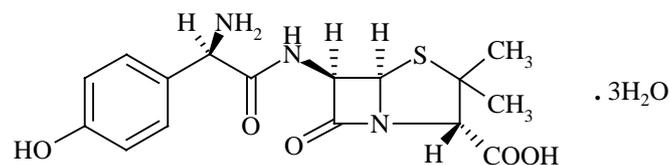
Active Ingredient: Amoxicillin trihydrate

Inactive Ingredients: Magnesium stearate, povidone, sodium starch glycolate, cellulose-microcrystalline, titanium dioxide, talc-purified and hypromellose.

## 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: (2S,5R,6R)-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: C<sub>16</sub>H<sub>19</sub>N<sub>3</sub>O<sub>5</sub>S.3H<sub>2</sub>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 micro-organisms. 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 (e.g. 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 1 to 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 vary and are dependant 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.

Efficacy of  $\beta$ -lactam antibiotic is related to the time in which the concentration of antibiotic at the site of infection exceeds the minimal inhibitory concentration (MIC) of that antibiotic for the pathogen. Analysis of pharmacokinetic data from a single dose study of the amoxicillin 500 mg capsule and a single dose study of the amoxicillin 1 g film-coated tablet showed that the mean amoxicillin plasma concentrations were above the (MIC) for similar proportions of the dose interval for the MIC levels of 0.5, 1.0 and 2.0  $\mu\text{g/mL}$ . The time above the MIC for other MIC levels and the time above MIC at steady state were not assessed for either formulation and/or dose regimen of amoxicillin.

Data to establish the bioequivalence of the 1 x 1000 mg tablet with 2 x 500 mg capsules have not been submitted and as such, the products should not be directly substituted.

### Clinical Trials

Amoxil Duo (1000 mg tablets bid) and amoxicillin (500 mg capsules tds ) were compared in a multi-centre, double-blind, randomised study of 395 adult patients with acute exacerbations of chronic bronchitis. Patients were treated for 10 days and were assessed during therapy (days 3 – 5), after the end of therapy (days 12 – 15) and at follow-up (days 28 – 35).

The statistical analysis for each clinical efficacy parameter during therapy (pooling moderate/severe severity and mucopurulent/purulent sputum appearance) is shown below:

	Amoxil Duo 1000 mg bid	Amoxicillin 500 mg tds	95% CI	Comparison X <sup>2</sup> Test
Impairment of subjective general state (moderate or severe)	24.6%	31.5%	-16.5%, 2.7%	p=0.15
Severity of cough (moderate or severe)	26.3%	40.7%	-24.4, -4.5%	p=0.005
Severity of dyspnoea (moderate or severe)	16.0%	22.2%	-14.6%, 2.2%	p=0.15
Severity of rales/rhonchi (moderate or severe)	11.5%	13.5%	-9.2%, 4.9%	p=0.55
Sputum appearance (mucopurulent or purulent)	32.5%	35.9%	-13.4%, 6.9%	p=0.53

The primary endpoint of this study was the clinical success at the end of therapy. For clinically evaluable patients, the clinical success rate at the end of therapy was 156/175 (89.1%) in the Amoxil Duo 1000 mg bid group and 150/162 (92.6%) in the amoxicillin 500 mg tds group. The results (p-value=0.27; CI 95%=-0.96%, 2.7%) confirm the equivalence in clinical efficacy between the two treatment groups. Bacteriological success was a secondary endpoint in this study. A total of 219 patients were eligible for assessment of bacteriological success at the end of treatment. Bacteriological success was achieved for 85/109 (78%) of patients given Amoxil Duo and 83/110 (75.5%) of patients given amoxicillin 500 mg tds.

Assessment at follow-up yielded a clinical recurrence rate of 13.4% in the bid group and 13.7% in the tds group. No statistically significant differences between the two treatment groups.

### INDICATIONS

Amoxil Duo is indicated in the treatment of acute exacerbation of chronic bronchitis.

#### Notes:

Therapy should be guided by bacteriologic 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 agent has yet to be identified.

Amoxil Duo 1000 mg tablets have not been shown to be bioequivalent to the 500 mg and 250 mg capsule formulations given in equivalent doses. Therefore, Amoxil Duo 1000 mg tablets and other forms of amoxicillin are not considered interchangeable.

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

### **CONTRAINDICATIONS**

Known and suspected hypersensitivity to penicillins. Potential cross allergy should be considered in patients with cephalosporin hypersensitivity.

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

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). 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.

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.

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.

Amoxycillin is not the treatment of choice in patients presenting with sore throat or pharyngitis due to the possibility of underlying infectious mononucleosis, in the presence of which, there is a high incidence of amoxycillin induced rash.

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

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 amoxycillin

#### **Use in Pregnancy: Category A**

Animal studies with amoxycillin have shown no teratogenic effects.

#### **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.

#### **Drug/Laboratory Interactions**

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 amoxycillin.

The concomitant administration of probenecid produces sustained and higher plasma levels by reducing renal elimination of amoxycillin.

Oral administration of amoxycillin will result in high urine concentrations of amoxycillin. Since high urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest, 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.

#### **ADVERSE REACTIONS**

Amoxycillin 1000 mg tablets twice daily and amoxycillin 500 mg capsules three times daily for ten days were compared in a study of 395 adult patients with acute exacerbations of chronic bronchitis. There were no significant differences on the incidence or severity of adverse events between the treatment groups.

The incidence of adverse events reported at a frequency of >1%, and possibly or probably drug related, is shown in the following table:

Adverse Event	No. of Reports (%)	
	1000 mg b.i.d. (n=197)	500 mg t.d.s. (n=198)
Gastro-intestinal		
Diarrhoea	8 (4.06)	12 (6.06)
Nausea	7 (3.55)	4 (2.02)
Abdominal Pain	4 (2.03)	1 (0.51)
Hypersensitivity		
Erythema	1 (0.51)	3 (1.52)
Exanthema	2 (1.02)	1 (0.51)
Resistance mechanism		
Candidiasis	1 (0.51)	2 (1.01)
Fungal/mycotic infection	3 (1.52)	0 (0)
Others	10 (5.08)	11 (5.56)
<b>Total</b>	<b>36 (18.27)</b>	<b>34 (17.17)</b>

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

*Gastrointestinal.* Nausea, vomiting, diarrhoea. Intestinal candidiasis and antibiotic associated colitis (including pseudomembranous colitis and haemorrhagic colitis) have been reported rarely (see Precautions).

*Hypersensitivity.* Erythematous maculopapular rash, pruritus and urticaria have been reported occasionally. Rarely, skin reactions such as erythema multiforme and Stevens-Johnson syndrome, toxic epidermal necrolysis and bullous and exfoliative dermatitis have been reported. As with other antibiotics, severe allergic reactions including angioneurotic oedema, anaphylaxis, serum sickness, hypersensitivity vasculitis and interstitial nephritis 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.

*Renal.* Crystalluria has 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.

As the blood-brain barrier becomes more permeable in meningitis, toxic symptoms may be precipitated by lower levels of amoxicillin in patients with meningitis.

**DOSAGE AND ADMINISTRATION**

Amoxil Duo may be taken without regard to food.

Adults: 1000 mg twice daily.

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.

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

**Dosage in patients with renal impairment**

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 dose.

**OVERDOSAGE**

Signs of overdosage of amoxycillin would predominantly 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 also refer to Precautions and Adverse Reactions.

**PRESENTATION**

Amoxil Duo tablets are oval, biconvex, white to cream-coloured, scored on both sides. Each tablet contains 1000 mg amoxycillin as the trihydrate.

Amoxil Duo are packed in blisters of 10, 14, 20 or 100 tablets. Starter packs of 2 tablets.

**Storage**

Store below 25°C, protect from moisture.

**SPONSOR**

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Date of TGA Approval: 5<sup>th</sup> July 2002

Date of last amendment: 5 February, 2004