AMOXIL

Amoxicillin trihydrate

QUALITATIVE AND QUANTITATIVE COMPOSITION

AMOXIL Capsules: Maroon and gold capsules (may be referred to as 'red and yellow' in some markets) over-printed with 'GS LEX' on the 250 mg and 'GS JVL' on the 500 mg.

AMOXIL Capsules 250 mg contain 250 mg amoxicillin per capsule.

AMOXIL Capsules 500 mg contain 500 mg amoxicillin per capsule.

AMOXIL Syrup and Syrup Forte: lemon-peach-strawberry flavoured suspensions. Presented as powder in bottles for preparing 60 mL or 100 mL.

AMOXIL Paediatric Suspension: Lemon-peach-strawberry flavoured suspensions. Presented as powder in bottles.

AMOXIL Syrup 125 mg contains 125 mg amoxicillin per 5 mL dose.

AMOXIL Syrup Forte 250 mg contains 250 mg amoxicillin per 5 mL dose.

AMOXIL Paediatric Suspension contains 125 mg amoxicillin per 1.25 mL dose.

The amoxicillin is present as the trihydrate in *AMOXIL* oral presentations.

CLINICAL INFORMATION

Indications

AMOXIL should be used in accordance with local official antibiotic-prescribing guidelines and local susceptibility data.

AMOXIL is a broad spectrum antibiotic indicated for the treatment of commonly occurring bacterial infections such as:

Upper respiratory tract infections e.g. ear, nose and throat infections, otitis media.

Lower respiratory tract infections e.g. acute exacerbations of chronic bronchitis, lobar and bronchopneumonia.

Gastrointestinal tract infections e.g. typhoid and paratyphoid fever.

Genito-urinary tract infections e.g. cystitis, urethritis, pyelonephritis, bacteriuria in pregnancy, septic abortion, puerperal sepsis.

Prophylaxis of endocarditis: *AMOXIL* may be used for the prevention of bacteraemia associated with procedures such as dental extraction, in patients at risk of developing

endocarditis (see Table in *Dosage and Administration*).

Skin and soft tissue infections.

Biliary tract infections.

Bone infections.

Pelvic infections.

Gonorrhoea (non-penicillinase producing strains).

Septicaemia.

Endocarditis.

Meningitis.

Peritonitis.

Dental abscess (as an adjunct to surgical management).

Helicobacter pylori eradication in peptic (duodenal and gastric) ulcer disease.

Infections such as septicaemia, endocarditis and meningitis due to susceptible organisms should be treated initially with high doses of a parenteral therapy and, where appropriate, in combination with another antibiotic.

Susceptibility to amoxicillin will vary with geography and time and local susceptibility data should be consulted where available and microbiological sampling and susceptibility testing performed where necessary (see *Pharmacodynamics*).

Dosage and Administration

Pharmaceutical Form: Capsule and Powder for suspension

Populations

- **Adult dosage (including elderly patients):**

Standard adult dosage: 250 mg 3 times daily, increasing to 500 mg 3 times daily for more severe infections.

High dosage therapy (maximum recommended oral dosage 6 g daily in divided doses): A dosage of 3 g twice daily is recommended in appropriate cases for the treatment of severe or recurrent purulent infection of the respiratory tract.

Short course therapy: Simple acute urinary tract infection: two 3 g doses with 10 to 12 hours between the doses. Dental abscess: two 3 g doses with 8 hours between the doses. Gonorrhoea: single 3 g dose.

Helicobacter eradication in peptic (duodenal and gastric) ulcer disease:

AMOXIL is recommended at a dose of twice daily in association with a proton pump inhibitor and antimicrobial agents as detailed below:

Omeprazole 40 mg daily, Amoxicillin 1 g twice a day, Clarithromycin 500 mg twice a day for 7 days.

or

Omeprazole 40 mg daily, Amoxicillin 750 mg to 1 g twice a day, Metronidazole 400 mg 3 times a day for 7 days.

- **Children's dosage (up to 10 years of age):**

Standard children's dosage: 125 mg 3 times daily, increasing to 250 mg 3 times daily for more severe infections.

AMOXIL Paediatric Suspension is recommended for children under 6 months of age.

In severe or recurrent acute otitis media, especially where compliance may be a problem, 750 mg twice a day for 2 days may be used as an alternative course of treatment in children aged 3 to 10 years. The use of *AMOXIL* 750 mg Sachets Syrup Forte is recommended.

- **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 dosage according to the following scheme:

Adults and Children over 40 kg:

Mild impairment (creatinine clearance greater than 30 mL/min)	- No change in dosage
Moderate impairment (creatinine clearance 10 to 30 mL/min)	- 500 mg twice a day maximum
Severe impairment (creatinine clearance less than 10 mL/min)	- 500 mg/day maximum

Children under 40 kg:

Mild impairment (creatinine clearance greater than 30 mL/min)	- No change in dosage
Moderate impairment (creatinine clearance 10 to 30 mL/min)	- 15 mg/kg twice a day (maximum 500 mg/twice daily)
Severe impairment (creatinine clearance less than 10 mL/min)	- 15 mg/kg once a day (maximum 500 mg)

Patients receiving peritoneal dialysis:

Dosing as for patients with severe renal impairment (creatinine clearance less than 10 mL/min). Amoxicillin is not removed by peritoneal dialysis.

Patients receiving haemodialysis:

Dosing as for patients with severe renal impairment (creatinine clearance less than 10 mL/min).

Amoxicillin is removed from the circulation by haemodialysis. Therefore, 1 additional dose (500 mg for adults or 15 mg/kg for children under 40 kg) may be administered

during dialysis and at the end of each dialysis.

Prophylaxis of endocarditis: see table below.

Prophylaxis of endocarditis:

Consideration should be given to official guidelines and/or hospital and dental formularies.

Prophylaxis of Endocarditis: Condition		**Adults and children over 40kg**	**Children under 40kg**
Dental procedures: In patients with the highest risk of infective endocarditis that require manipulation of the gingival or periapical region of the teeth, or perforation of the oral mucosa.	Patients not having general anaesthetic.	2 g as a single oral dose 30 to 60 minutes before procedure.	50 mg/kg as a single oral dose 30 to 60 minutes before procedure.

Parenteral therapy is indicated if the oral route is considered impracticable or unsuitable, and particularly for the urgent treatment of severe infection.

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.

Contraindications

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

Warnings and Precautions

Before initiating therapy with *AMOXIL*, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins or cephalosporins.

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of hypersensitivity to beta-lactam antibiotics (see *Contraindications*). Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to amoxicillin (*see Adverse Reactions*). If an allergic reaction occurs, *AMOXIL* should be discontinued and appropriate alternative therapy instituted.

Serious anaphylactic reactions may require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management, including intubation, may also be required.

Amoxicillin should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.

Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.

Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving *AMOXIL* 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.

Dosage should be adjusted in patients with renal impairment (see *Dosage and Administration*).

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria (see *Overdose*).

AMOXIL Paediatric Suspension contains sodium benzoate. It may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

AMOXIL suspensions may contain aspartame, which is a source of phenylalanine and so should be used with caution in patients with phenylketonuria.

Interactions

Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use with *AMOXIL* may result in increased and prolonged blood levels of amoxicillin.

Concurrent administration of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

It is recommended that when testing for the presence of glucose in urine during *AMOXIL* treatment, enzymatic glucose oxidase methods should be used. Due to the high urinary concentrations of amoxicillin, false positive readings are common with chemical methods.

In common with other antibiotics, *AMOXIL* may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

In the literature, there are rare cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of *AMOXIL*.

Pregnancy and Lactation

Pregnancy

The safety of this medicinal product for use in human pregnancy has not been established by well-controlled studies in pregnant women. Reproduction studies have been performed in mice and rats at doses of up to 10 times the human dose and these studies have revealed no evidence of impaired fertility or harm to the foetus due to amoxicillin. *AMOXIL* may be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Lactation

AMOXIL may be given during lactation. With the exception of the risk of sensitisation associated with the excretion of trace quantities of amoxicillin in breast milk, there are no known detrimental effects for the breast-fed infant.

Effects on Ability to Drive and Use Machines

Adverse effects on the ability to drive or operate machinery have not been observed.

Adverse Reactions

The following convention has been utilised for the classification of undesirable effects: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

The majority of the side effects listed below are not unique to *AMOXIL* and may occur when using other penicillins.

Unless otherwise stated, the frequency of adverse events (AEs) has been derived from more than 30 years of post-marketing reports.

Blood and lymphatic system disorders

Very rare:	Reversible leucopenia (including severe neutropenia or agranulocytosis), reversible thrombocytopenia and haemolytic anaemia.
	Prolongation of bleeding time and prothrombin time.

Immune system disorders

Very rare:	As with other antibiotics, severe allergic reactions, including angioneurotic oedema, anaphylaxis (see *Warnings and Precautions*), serum sickness and hypersensitivity vasculitis.

If a hypersensitivity reaction is reported, the treatment must be discontinued (see also *Skin and subcutaneous tissue disorders*).

Nervous system disorders

Very rare:	Hyperkinesia, dizziness, aseptic meningitis, convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Cardiac disorders

Very rare	Kounis syndrome (see *Warnings and Precautions*).

Infections and infestations

Very rare:	Mucocutaneous candidiasis.

Gastrointestinal disorders

#Common:	Diarrhoea and nausea.
#Uncommon:	Vomiting.
Very rare:	Antibiotic associated colitis (including pseudomembranous colitis and haemorrhagic colitis; see *Warnings and Precautions*).
	Black hairy tongue.
	Superficial tooth discolouration has been reported in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing ***(for suspension formulations only)***.

Hepatobiliary disorders

Very rare:	Hepatitis and cholestatic jaundice. A moderate rise in AST and/or ALT.

The significance of a rise in AST and/or ALT is unclear.

Skin and subcutaneous tissue disorders

#Common:	Skin rash.

#Uncommon:	Urticaria and pruritus.
Very rare:	Skin reactions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous and exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS). (See also *Immune system disorders*).

Renal and urinary tract disorders

Very rare:	Interstitial nephritis, crystalluria (see *Overdose*).

#The incidence of these AEs was derived from clinical studies involving a total of approximately 6,000 adult and paediatric patients taking amoxicillin.

Overdose

Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and symptoms of water/electrolyte imbalance should be treated symptomatically. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see *Warnings and Precautions*).

AMOXIL can be removed from the circulation by haemodialysis.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC Code

Pharmacotherapeutic group: penicillins with extended spectrum

ATC Code: J01CA04

Amoxicillin is a semi-synthetic aminopenicillin of the beta-lactam group of antibiotics. It has a broad spectrum of antibacterial activity against many Gram-positive and Gram-negative micro-organisms, acting through the inhibition of biosynthesis of cell wall mucopeptide. Amoxicillin is, however, susceptible to degradation by beta-lactamases and therefore the spectrum of activity does not include organisms which produce these enzymes including resistant staphylococci, and all strains of *Pseudomonas, Klebsiella* and *Enterobacter*.

It is rapidly bactericidal and possesses the safety profile of a penicillin.

The prevalence of acquired resistance is geographically and time-dependent and for select species may be very high. Local information on resistance is desirable, particularly when treating severe infections.

***In vitro* susceptibility of micro-organisms to Amoxicillin** †Natural intermediate susceptibility in the absence of acquired mechanism of resistance.
Commonly Susceptible Species
Gram-positive aerobes: *Bacillus anthracis* *Enterococcus faecalis* *Beta-hemolytic streptococci* *Listeria monocytogenes*
Gram-negative aerobes: *Bordetella pertussis*
Other: *Leptospira icterohaemorrhagiae* *Treponema pallidum*
Species for which acquired resistance may be a problem
Gram-negative aerobes: *Escherichia coli* *Haemophilus influenzae* *Helicobacter pylori* *Proteus mirabilis* *Salmonella* spp. *Shigella* spp. *Neisseria gonorrhoeae* *Pasteurella* spp. *Vibrio cholerae*
Gram-positive aerobes: *Coagulase-negative staphylococcus* *Corynebacterium* spp. *Staphylococcus aureus* *Streptococcus pneumoniae* *Viridans group streptococcus*

Gram-positive anaerobes: *Clostridium* spp.
Gram-negative anaerobes: *Fusobacterium* spp.
Other: *Borrelia burgdorferi*
Inherently resistant organisms
Gram-positive aerobes: *Enterococcus faecium†*
Gram-negative aerobes: *Acinetobacter* spp. *Enterobacter* spp. *Klebsiella* spp. *Pseudomonas* spp.
Gram-negative anaerobes: *Bacteroides* spp. (many strains of *Bacteroides fragilis* are resistant).
Other: *Chlamydia* spp. *Mycoplasma* spp. *Legionella* spp.

Pharmacokinetics

Amoxicillin is well-absorbed. Oral administration, usually at convenient three times daily dosage, produces high serum levels independent of the time at which food is taken. Amoxicillin gives good penetration into bronchial secretions and high urinary concentrations of unchanged antibiotic.

Amoxicillin is not highly protein bound; approximately 18% of total plasma drug content is bound to protein. Amoxicillin diffuses readily into most body tissues and fluids, with the exception of the brain and spinal fluid. Inflammation generally increases the permeability of the meninges to penicillins and this may apply to *AMOXIL*.

The major route of elimination for amoxicillin is via the kidney. Approximately 60 to 70% of amoxicillin is excreted unchanged in urine during the first six hours after administration of a standard dose. The elimination half-life is approximately one hour.

Amoxicillin is also partly excreted in the urine as the inactive penicilloic acid in

quantities equivalent to 10 to 25% of the initial dose.

Concurrent administration of probenecid delays amoxicillin excretion.

PHARMACEUTICAL INFORMATION

List of Excipients

Capsules:

Magnesium stearate, Erythrosine BS (E127), Indigo Carmine (E132), Titanium Dioxide (E171), Yellow Iron Oxide (E172)

250 mg/5 mL, 125 mg/5 mL, 125 mg/1.25 mL suspensions:

Carboxymethylcellulose Sodium, Lemon-Peach-Strawberry Dry Flavour, Aspartame, Sodium Benzoate, Crospovidone, Xanthan Gum, Silica Hydrophobic Colloidal, Magnesium Stearate

Shelf Life

The expiry date is indicated on the packaging.

The reconstituted suspension should be used within 14 days.

Storage

The storage conditions are detailed on the packaging.

Keep out of reach of children.

All presentations should be stored in a dry place.

For storage condition of reconstituted *AMOXIL* suspension, refer to the packaging.

Nature and Contents of Container

Capsules:

PVC/Aluminium blister pack

Use and Handling

Directions for making up the suspension:
• Check cap seal is intact before use.
• Invert and shake bottle to loosen powder.
• Fill the bottle with water to just below the mark on bottle label.
• Invert and shake well, then top up with water to the mark. Invert and shake again.
• Shake well before taking each dose.

Not all presentations are available in every country.

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