Clamoxyl 500 mg Capsule

Amoxicillin trihydrate

QUALITATIVE AND QUANTITATIVE COMPOSITION

CLAMOXYL 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:

CLAMOXYL Capsules 500 mg contain 500 mg amoxicillin per capsule.

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

CLINICAL INFORMATION

Indications

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

CLAMOXYL 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 exacerbation of chronic obstructive pulmonary disease (AECOPD)/acute exacerbations of chronic bronchitis (AECB), 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.
- Other infections including borreliosis (*Borrelia burgdorferi*) (Lyme disease)
- prophylaxis of endocarditis: amoxicillin may be used for the prevention of bacteraemia associated with the development of endocarditis (see table in *Populations* for dosage details).
- 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

Populations

- **Adults and children over 40 kg:**

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.

Eradication of H. pylori: amoxicillin 750 mg to 1 g twice daily in combination with a proton pump inhibitor (e.g. omeprazole, lansoprazole) and another antibiotic (e.g. clarithromycin, metronidazole) for 7 days.

- **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	- 500 mg/day maximum

less than 10 mL/min)

Patients receiving peritoneal dialysis:

Amoxicillin maximum 500 mg/day. 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) 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 40 kg**
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.

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

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 *CLAMOXYL***,** 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*). Drug-induced enterocolitis syndrome has been reported mainly in children receiving *CLAMOXYL* (see *Adverse Reactions*). Drug-induced enterocolitis syndrome is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after medicinal product administration) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, lethargy, diarrhoea, hypotension or leucocytosis with neutrophilia. In severe cases, drug-induced enterocolitis syndrome can progress to shock. If an allergic reaction occurs, *CLAMOXYL* 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.

*CLAMOXY*L 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 *CLAMOXYL* 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*).

Interactions

Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use with *CLAMOXYL* 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 *CLAMOXYL* 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, *CLAMOXYL* 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 *CLAMOXYL*.

Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

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

Lactation

CLAMOXYL 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 *CLAMOXYL* 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.

Infections and infestations

Very rare:	Mucocutaneous candidiasis

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*).

Gastrointestinal disorders

#Common:	Diarrhoea and nausea.
#Uncommon:	Vomiting.
Very rare:	Antibiotic associated colitis (including pseudomembraneous colitis and haemorrhagic colitis), drug-induced enterocolitis syndrome (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), drug reaction with eosinophilia and systemic symptoms (DRESS) and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome)(see also *Immune system disorders*) and linear IgA disease.

Renal and urinary 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).

CLAMOXYL 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** Where clinical efficacy of amoxicillin has been demonstrated in clinical trials this is indicated with an asterisk (*). †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).
Others: *Chlamydia* spp. *Mycoplasma* spp. *Legionella* spp.

Pharmacokinetics

Amoxicillin is well absorbed. Oral administration, usually at convenient three times a day 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 *CLAMOXYL.*

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.

Small amounts of the drug are also excreted in faeces and bile.

PHARMACEUTICAL INFORMATION

List of Excipients

Capsules:

Magnesium stearate

Shelf-Life

The expiry date is indicated on the packaging.

Storage

The storage conditions are detailed on the packaging.

Keep out of reach of children.

Should be stored in a dry place.

Nature and Contents of Container

Capsules:

Blister packs made of PVC or PVC-PVdC film and aluminium foil coated with a heat-sealing lacquer

Incompatibilities

Not known.

Manufactured by:

Glaxo Wellcome Production

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