

Approved Professional Information for Medicines for Human Use:

AMOXYCILLIN AUSTELL

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

AMOXYCILLIN 250 mg AUSTELL CAPSULES

AMOXYCILLIN 500 mg AUSTELL CAPSULES

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AMOXYCILLIN 250 mg AUSTELL Capsules

Each capsule contains Amoxicillin Trihydrate equivalent to Amoxicillin 250 mg.

Sugar free

AMOXYCILLIN 500 mg AUSTELL Capsules

Each capsule contains Amoxicillin Trihydrate equivalent to Amoxicillin 500 mg.

Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules.

AMOXYCILLIN 250 mg AUSTELL capsules

White to creamish white in powder/plug form enclosed in red / buff hard gelatin capsule size '2'
with "AMOXY 250" printing in black ink.

AMOXYCILLIN 500 mg AUSTELL capsules

White to creamish white in powder/plug form enclosed in red / buff hard gelatin capsule of size '0' with "AMOXY 500" printing in black.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AMOXYCILLIN AUSTELL formulations are indicated for the treatment of mild to moderately severe infections caused by susceptible organisms:

- Upper respiratory tract infections such as sinusitis, otitis media, tonsillitis.
- Lower respiratory tract infections such as bronchitis, lobar and bronchopneumonia.
- Gastro-intestinal infections such as typhoid fever.
- Other infections including Borreliosis (Lyme disease).
- In the following infections, Amoxicillin therapy should be initiated only if there is microbiological evidence that the causative organism is sensitive to Amoxicillin:
 - Skin and soft tissue infections.
 - Urinary tract infections: cystitis, urethritis, pyelonephritis, bacteriuria in pregnancy.
- "As part of combination therapy in established *Helicobacter pylori* infection, associated with duodenal ulceration."
- Prophylaxis of endocarditis.

4.2 Posology and method of administration

Posology

The total daily dose as below is administered in divided doses. The most common regimen is 8 hourly.

Oral administration

Treatment should be continued for 48 to 72 hours beyond the time that a clinical response has been obtained. It is recommended that at least 10 days treatment be given for any infection

Austell Pharmaceuticals (Pty) Ltd, 370003-4, Amoxicillin 250/500 Austell, Capsules and 250/500 mg caused by beta-haemolytic streptococci to prevent the occurrence of acute rheumatic fever or glomerulonephritis.

The absorption of AMOXYCILLIN AUSTELL is not affected significantly when taken with food.

Adults and children over 40 kg

Total daily dosage of 750 mg to 3 g administered in divided doses. Maximum recommended dose: 6 g/day in divided doses.

Respiratory tract infections: 500 mg administered 8 hourly.

Lyme disease: 4 g/day in isolated erythema chronicum migrans and 6 g/day in the case of generalized manifestations, both for a minimum of 12 days.

Gonorrhoea: 3 g with 1 g probenecid

Eradication of Helicobacter pylori: 750 mg – 1 g in combination treatment given 12 hourly for the eradication of established H pylori infection associated with duodenal ulceration for seven days.

Children under 40 kg

20-50 mg/kg/day in divided doses.

Maximum recommended dose: 150 mg/kg/day in divided doses.

Lyme disease: 20-50 mg/kg/day in isolated erythema chronicum migrans and 100 mg/kg/day in the case of generalized manifestations, both for a minimum of 12 days.

Elderly

No adjustment needed: as for adults unless there is evidence of severe renal impairment (see below).

Renal impairment:

Glomerular filtration rate >30 ml/min: No adjustment needed.

Glomerular filtration rate 10-30 ml/min: Maximum 500 mg 12 hourly.

Glomerular filtration rate <10 ml/min: Maximum 500 mg daily.

In patients receiving peritoneal dialysis: Maximum 500 mg daily.

Method of administration

AMOXYCILLIN AUSTELL is for oral administration.

4.3 Contraindications

- Hypersensitivity to the amoxicillin trihydrate, to any of the penicillins or to any of the excipients listed in section 6.1.
- Hypersensitivity to penicillins or to cephalosporins. Cross-sensitivity between penicillins and cephalosporins is well documented.
- History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam medicine (e.g. a cephalosporin, carbapenem or monobactam).
- AMOXYCILLIN AUSTELL should not be given to patients with infectious mononucleosis, since they are especially susceptible to amoxicillin-induced skin rashes, patients with lymphatic leukaemia and patients with hyperuricaemia being treated with allopurinol, may be at increased risk of developing skin rashes.

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Before initiating therapy with amoxicillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam medicines (see sections 4.3 and 4.8).

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous reactions) have been reported in patients on penicillin therapy. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). These reactions are more likely to occur in individuals with

a history of penicillin and in atopic individuals. If an allergic reaction occurs, amoxicillin therapy must be discontinued and appropriate alternative therapy instituted.

Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin (see section 4.8). DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after drug administration) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, diarrhoea, hypotension or leucocytosis with neutrophilia. There have been severe cases including progression to shock.

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 (see section 5. 1). This particularly applies when considering the treatment of patients with urinary tract infections and severe infections of the ear, nose and throat.

Convulsions

Convulsions may occur in patients with impaired renal function or in those receiving high doses or in patients with predisposing factors (e.g. history of seizures, treated epilepsy or meningeal disorders (see section 4.8).

Renal impairment

In patients with renal impairment, the dose should be adjusted according to the degree of impairment (see section 4.2).

Skin reactions

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP, see section

4.8). This reaction requires amoxicillin discontinuation and contra-indicates any subsequent administration.

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.

Jarisch-Herxheimer reaction

The Jarisch-Herxheimer reaction has been seen following amoxicillin treatment of Lyme disease (see section 4.8). It results directly from the bactericidal activity of amoxicillin on the causative bacteria of Lyme disease, the spirochaeta *Borrelia burgdorferi*. Patients should be reassured that this is a common and usually self-limiting consequence of antibiotic treatment of Lyme disease.

Overgrowth of non-susceptible microorganisms

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

Antibiotic-associated colitis has been reported with nearly all antibacterial medicines and may range in severity from mild to life threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during, or subsequent to, the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin should immediately be discontinued, a medical practitioner consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contra-indicated in this situation.

Prolonged therapy

Periodic assessment of organ system functions; including renal, hepatic and haematopoietic function is advisable during prolonged therapy. Elevated liver enzymes and changes in blood counts have been reported (see section 4.8).

Anticoagulants

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin.

Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly.

Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see section 4.5 and 4.8).

Crystalluria

In patients with reduced urine output, crystalluria (including acute renal injury) 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. In patients with bladder catheters, a regular check of patency should be maintained (see sections 4.8 and 4.9).

Interference with diagnostic tests

Elevated serum and urinary levels of amoxicillin are likely to affect certain laboratory tests. Due to the high urinary concentrations of amoxicillin, false positive readings are common with chemical methods.

It is recommended that when testing for the presence of glucose in urine during amoxicillin treatment, enzymatic glucose oxidase methods should be used.

The presence of amoxicillin may distort assay results for oestriol in pregnant women.

4.5 Interaction with other medicines and other forms of interaction

Probenecid decreases the renal tubular secretion of AMOXYCILLIN AUSTELL. Concurrent use with AMOXYCILLIN AUSTELL may result in increased and prolonged blood concentrations of AMOXYCILLIN AUSTELL

AMOXYCILLIN AUSTELL may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

The concomitant administration of allopurinol and ampicillin substantially increases the incidence of skin rashes in patients receiving both medicines as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the

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hyperuricaemia present in these patients.

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

Interaction with Laboratory tests

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

Oral anticoagulants

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of
interaction. However, in the literature there are 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 amoxicillin. Moreover, adjustments in the
dose of oral anticoagulants may be necessary (see sections 4.4 and 4.8).

Methotrexate

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of AMOXYCILLIN AUSTELL in pregnancy has not been established.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive
toxicity. Limited data on the use of amoxicillin during pregnancy in humans do not indicate an
increased risk of congenital malformations.

Breastfeeding

AMOXYCILLIN AUSTELL is distributed into breast milk. Although significant problems in humans have not been documented, the use of AMOXYCILLIN AUSTELL by nursing mothers may lead to sensitization, diarrhoea, candidiasis and skin rash in the infant, so that breast-feeding might have to be discontinued.

Fertility

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

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with amoxicillin.

| System Organ Class | Frequency | | |
|--------------------------------------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| | Frequent | Less Frequent | Not known |
| Infections and infestations | -- | Mucocutaneous candidiasis | -- |
| Blood and lymphatic system disorders | -- | Reversible leucopenia (including severe neutropenia or agranulocytosis), reversible thrombocytopenia and haemolytic anaemia. Prolongation of bleeding time and prothrombin time (see section 4.4). | -- |
| Immune system disorders | -- | Severe allergic reactions, including angioneurotic oedema, anaphylaxis, serum sickness and hypersensitivity vasculitis (see section 4.4). | Jarisch-Herxheimer reaction (see section 4.4). |
| Nervous system disorders | -- | Hyperkinesia, dizziness and convulsions (see section 4.4). Headache. | Aseptic meningitis |
| Cardiac disorders | -- | -- | Kounis syndrome |

| | | | |
|----------------------------------------|------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| Gastrointestinal disorders | *Diarrhoea and nausea Indigestion, abdominal pain | *Vomiting Antibiotic associated colitis (including pseudomembranous colitis and haemorrhagic colitis see section 4.4). Black hairy tongue | Drug-induced enterocolitis syndrome |
| Hepatobiliary disorders | -- | Hepatitis and cholestatic jaundice. A moderate rise in AST and/or ALT. | -- |
| Skin and subcutaneous tissue disorders | *Skin rash | *Urticaria and pruritus Skin reactions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous and exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP) (see section 4.4) and drug reaction with eosinophilia and systemic symptoms (DRESS). | Linear IgA disease |
| Renal and urinary disorders | -- | Interstitial nephritis | Crystalluria (including acute renal injury) |
| <u>Miscellaneous</u> | == | Superficial tooth discolouration | == |

*The incidence of these AEs was derived from clinical studies involving a total of approximately 6,000 adult and

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paediatric patients taking amoxicillin.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za

4.9 Overdose

Symptoms and signs of overdose:

Gastrointestinal symptoms (such as nausea, vomiting and diarrhoea) and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4). Convulsions may occur in patients with impaired renal function or in those receiving high doses (see sections 4.4 and 4.8).

Treatment of intoxication

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin can be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 20.1.2 Penicillins

Pharmacotherapeutic group: Penicillins with extended spectrum

ATC Code: J01CA04

Mechanism of action

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce

these enzymes.

Pharmacokinetic/pharmacodynamic relationship

The time above the minimum inhibitory concentration ($T > MIC$) is considered to be the major determinant of efficacy for amoxicillin.

Mechanisms of resistance

The main mechanisms of resistance to amoxicillin are:

- Inactivation by bacterial beta-lactamases.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

Amoxicillin is a semisynthetic beta-lactamase-susceptible penicillin, which has in vitro bactericidal activity against broad spectrum of non-beta-lactamase-producing Gram positive and Gram negative organisms. The spectrum of activity does not include those organisms that produce beta lactamases, namely resistant staphylococci, and all strains of Pseudomonas, Klebsiella and Enterobacter.

The following organisms are generally sensitive to the bactericidal action of Amoxicillin in vitro. In vitro sensitivity does not mean in vivo efficacy [(*) denotes sensitivity tests must be performed].

Gram positive bacteria

*Staphylococcus aureus (Penicillin-sensitive)**

Streptococcus pyogenes

*Streptococcus viridans**

*Streptococcus faecalis**

*Streptococcus Pneumoniae**

*Corynebacterium species**

*Clostridium species**

*Bacillus anthracis**

Listeria monocytogenes

Gram negative bacteria

Neisseria meningitidis *(except the carrier state)

*Neisseria gonorrhoeae**

*Haemophilus influenza**

Bordetella pertussis

*Escherichia coli**

*Salmonella species**

*Shigella species**

*Proteus mirabilis**

*Pasteurella multocida**

*Fusabacterium species**

Helicobacter pylori

Leptospira species

5.2 Pharmacokinetic properties

Absorption

Amoxicillin is stable in the presence of acidic gastric secretions. Peak blood levels are achieved 1-2 hrs after administration. There is a linear dose response in peak serum levels.

Food does not interfere with the absorption of Amoxicillin.

Distribution

Approximately 18 % of the total plasma Amoxicillin content is protein bound. Amoxicillin diffuses

readily into most body tissues with the exception of the brain and spinal fluid. Inflammation generally increases the permeability of the meninges to penicillins and this may apply to Amoxicillin%.

Biotransformation

There is no evidence that alendronate is metabolised in animals or humans.

Elimination

The elimination half-life is approximately 1 hour. Amoxicillin is primarily excreted via the kidneys. Small amounts of the drug are also excreted in the faeces and bile. Amoxicillin crosses the placenta and is distributed into breast milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Amoxicillin 250 mg Austell capsules

Magnesium stearate

The composition of the hard gelatin capsule shell is: Gelatin, purified water, SLS, methyl paraben, propyl paraben, titanium dioxide (E 171), brilliant blue (E 133), carmoisine (E 122), sunset yellow (E 110), quinoline yellow (E 104).

Amoxicillin 500 mg Austell Capsules

Magnesium stearate

The composition of the hard gelatin capsule shell is: Gelatin, purified water, SLS, methyl paraben, propyl paraben, titanium dioxide (E 171), brilliant blue (E 133), carmoisine (E 122), sunset yellow (E 110), quinoline yellow (E 104).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister pack in the carton until required for use.

Keep the container well closed.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

AMOXYCILLIN 250 mg AUSTELL:

Blister pack (Clear PVC film, Aluminium foil) of 1 x 15, 1 x 21, 3 x 10, 2 x 15 and 10 x 10 capsules.

Container of 500 capsules packed in HDPE bags.

AMOXYCILLIN 500 mg AUSTELL:

Blister pack (Clear PVC film, Aluminium foil) of 1 x 15, 1 x 21, 3 x 10, 2 x 15 and 10 x 10 capsules.

Container of 500 capsules packed in HDPE bags.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBER(S)

AMOXYCILLIN 250 mg AUSTELL: 37/20.1.2/0003

AMOXYCILLIN 500 mg AUSTELL: 37/20.1.2/0004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 September 2005

10. DATE OF REVISION OF THE TEXT

24 February 2025