

APPROVED PROFESSIONAL INFORMATION

AZITHROMYCIN 500 mg AUSTELL TABLETS

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

AZITHROMYCIN 500 mg AUSTELL Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains Azithromycin dihydrate equivalent to 500 mg azithromycin.

Contains sugar (lactose monohydrate)

Each film-coated tablet contains 3 mg lactose monohydrate.

3. PHARMACEUTICAL FORM

Film-coated tablets

AZITHROMYCIN 500 mg AUSTELL tablets are capsule shaped, white scored film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AZITHROMYCIN AUSTELL is indicated for the treatment of the following conditions in adult and children one year and older.

- lower respiratory tract infections such as bronchitis and pneumonia caused by sensitive *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus* or *Streptococcus pneumoniae*.
- upper respiratory tract infections such as sinusitis or pharyngitis caused by sensitive *Haemophilus influenzae*, *Staphylococcus aureus* or *Streptococcus pneumoniae*.
- uncomplicated skin and soft tissue infections caused by sensitive *Staphylococcus aureus*.
- uncomplicated genital tract infections caused by sensitive *Chlamydia trachomatis*.

For children 1 year and older, **AZITHROMYCIN AUSTELL** is indicated for the treatment of pharyngitis/tonsillitis and otitis media caused by susceptible organisms.

4.2 Posology and method of administration

Posology

Susceptible bacterial infections except sexually transmitted diseases.

Oral:

Adults and children over 45 kg in weight: 500 mg once daily for three days.

Over five days dosage regimen:

Day 1, 500 mg, and then 250 mg daily on days 2-5.

Sexually transmitted disease caused by *Chlamydia trachomatis*:

Adults: 1 g given as a single dose.

The normal adult dose is recommended for use in the elderly patient.

Special populations

Paediatric population

The safety and efficacy of **AZITHROMYCIN AUSTELL** in children under 1 year of age has not been established.

The tablet formulation is not suitable for children under 45 kg in weight.

Method of administration

Swallow tablets whole with some water. **AZITHROMYCIN AUSTELL** may be taken with or without meals.

4.3 Contraindications

- Hypersensitivity to the azithromycin, macrolide antibiotics or to any of the excipients listed in section 6.1.
- Co-administration with ergot alkaloids.
- Liver function impairment-Since biliary excretion is the major route of elimination.
- Pregnancy and lactation (see section 4.6)
- Children under 1 year of age has not been established.

4.4 Special warnings and precautions for use

Hypersensitivity

As with erythromycin and other macrolides, rare serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal), dermatologic reactions including acute generalised exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

Hepatotoxicity

Since the liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin (see section 4.8). Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.

In case of signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests/ investigations should be performed immediately. Azithromycin administration should be stopped if liver dysfunction has emerged.

Ergot derivatives

In patients receiving ergot derivatives, ergotism has been precipitated by co-administration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergotamine derivatives and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered (see section 4.5).

Prolongation of the QT interval

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarisation (see section 4.8); therefore caution is required when treating patients:

- With congenital or documented QT prolongation.
- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of classes I a and III, cisapride and terfenadine.
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

Superinfection:

As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms including fungi recommended.

***Clostridium difficile* associated diarrhoea**

Clostridium difficile associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhoea to fatal colitis.

Strains of *C. difficile* producing hypertoxins A and B contribute to the development of CDAD.

Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. Therefore, CDAD must be considered in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. Discontinuation of therapy with azithromycin and the administration of specific treatment for *C. difficile* should be considered.

Streptococcal infections

Penicillin is usually the first choice for treatment of pharyngitis/tonsillitis due to *Streptococcus pyogenes* and also for prophylaxis of acute rheumatic fever. Azithromycin is in general effective against streptococcus in the oropharynx, but no data are available that demonstrate the efficacy of azithromycin in preventing acute rheumatic fever.

Renal impairment

In patients with severe renal impairment (GFR < 10 ml/min) a 33% increase in systemic exposure to azithromycin was observed (see section 5.2).

Myasthenia gravis

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy (see section 4.8).

Co-administration with hydroxychloroquine or chloroquine

Carefully consider the balance of benefits and risks before prescribing azithromycin for any patients taking hydroxychloroquine or chloroquine, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality (see section 4.5).

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use of **AZITHROMYCIN AUSTELL** with:-

Antacids: In a pharmacokinetic study investigating the effects of simultaneous administration of antacids with azithromycin, no effect on overall bioavailability was seen, although peak serum concentrations were reduced by approximately 24%. In patients receiving both azithromycin and antacids, the medicine should not be taken simultaneously

Cetirizine: In healthy volunteers, coadministration of a 5-day regimen of azithromycin with 20 mg cetirizine at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.

Didanosine (Dideoxyinosine): Coadministration of 1200 mg/day azithromycin with 400 mg/day didanosine in 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

Digoxin and colchicine: Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin and colchicine, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and P-glycoprotein substrates such as digoxin are administered concomitantly, the possibility of elevated serum digoxin concentrations should be considered. Clinical monitoring, and possibly serum digoxin levels, during treatment with azithromycin and after its discontinuation are necessary.

Zidovudine: Single 1000 mg doses and multiple 1200 mg or 600 mg doses of azithromycin had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear, but it may be of benefit to patients.

Azithromycin does not interact significantly with the hepatic cytochrome P450 system. It is not believed to undergo the pharmacokinetic drug interactions as seen with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inactivation via cytochrome-metabolite complex does not occur with azithromycin.

Ergot derivatives: Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended (see section 4.4).

Pharmacokinetic studies have been conducted between azithromycin and the following medicines known to undergo significant cytochrome P450 mediated metabolism.

Atorvastatin: Coadministration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase-inhibition assay).

Carbamazepine: In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.

Cimetidine : In a pharmacokinetic study investigating the effects of a single dose of cimetidine, given 2 hours before azithromycin, on the pharmacokinetics of azithromycin, no alteration of azithromycin pharmacokinetics was seen.

Coumarin-Type Oral Anticoagulants: In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single dose of 15 mg warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to coadministration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Ciclosporin: In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of ciclosporin, the resulting ciclosporin C_{max} and AUC₀₋₅ were found to be significantly elevated (by 24 % and 21 % respectively), however no significant changes were seen in AUC_{0-∞}. Consequently, caution should be exercised before considering concurrent administration of these medicines. If coadministration of these medicines are necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

Efavirenz: Coadministration of a single dose of 600 mg azithromycin and 400 mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions.

Fluconazole: Coadministration of a single dose of 1200 mg azithromycin did not alter the pharmacokinetics of a single dose of 800 mg fluconazole. Total exposure and half-life of azithromycin were unchanged by the coadministration of fluconazole, however, a clinically insignificant decrease in C_{max} (18%) of azithromycin was observed.

Indinavir: Coadministration of a single dose of 1200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

Methylprednisolone: In a pharmacokinetic interaction study in healthy volunteers, azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.

Nelfinavir: Coadministration of azithromycin (1200 mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment was required.

Rifabutin: Coadministration of azithromycin and rifabutin did not affect the serum concentrations of either drug.

Neutropenia was observed in subjects receiving concomitant treatment of azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established (see section 4.8).

Sildenafil: In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3days) on the AUC and C_{max} of sildenafil or its major circulating metabolite.

Terfenadine: Pharmacokinetic studies have reported no evidence of an interaction between azithromycin and terfenadine. There have been rare cases reported where the possibility of such an interaction could not be entirely excluded; however there was no specific evidence that such an interaction had occurred.

Theophylline: There is no evidence of a clinically significant pharmacokinetic interaction when azithromycin and theophylline are co-administered to healthy volunteers.

Triazolam: In 14 healthy volunteers, coadministration of azithromycin 500 mg on Day 1 and 250 mg on Day 2 with 0,125 mg triazolam on Day 2 had no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo.

Trimethoprim/sulfamethoxazole: Coadministration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days with azithromycin 1200 mg on Day 7 had no significant effect on peak concentrations, total exposure or urinary excretion of either trimethoprim or sulfamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies.

Hydroxychloroquine and chloroquine: Observational data have shown that co-administration of azithromycin with hydroxychloroquine in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality. Carefully consider the balance of benefits and risks before prescribing azithromycin for any patients taking hydroxychloroquine. Similar careful consideration of the balance of benefits and risk should also be under taken before prescribing azithromycin for any patients taking chloroquine, because of the potential for a similar risk with chloroquine.

4.6 Fertility, pregnancy and lactation

Pregnancy and lactation

Safety and efficacy in pregnancy and lactation has not been established (see section 4.3).

Fertility

No data on fertility is available.

4.7 Effects on ability to drive and use machines

No data are available regarding the influence of azithromycin on a patient's ability to drive or operate machinery.

However, the possibility of undesirable effects like dizziness and convulsions should be taken into account when performing these activities.

4.8 Undesirable effects

System Organ Class	Frequency		
	Frequent	Less Frequent	Not known
Infections and infestations		candidiasis, oral candidiasis, vaginal infection	Pseudomembranous colitis
Blood and lymphatic system disorders		neutropenia. leukopenia	thrombocytopenia, haemolytic anaemia
Immune system disorders		angioedema, hypersensitivity, allergic reactions (difficulty in breathing, swelling of face, mouth, neck, hands and feet, arthralgia, urticaria, photosensitivity, skin rash, anaphylaxis).	anaphylactic reaction
Metabolism and nutrition disorders	anorexia		

Psychiatric disorders		Aggression anxiety	
Nervous system disorders	dizziness, headache, paraesthesia, dysgeusia	tinnitus, hearing loss, convulsions, somnolence, vertigo, fatigue, asthenia,	
		Syncope, convulsion, psychomotorhyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis (see section 4.4)	
Eye disorders	visual impairment		
Ear and labyrinth disorders	deafness	hearing impaired, tinnitus, vertigo	
Cardiac disorders		palpitations, arrhythmias including ventricular tachycardia, chest pain.	
		Torsades de pointes(see section 4.4)arrhythmia (see section4.4) including ventricular tachycardia.	
Vascular disorders			hypotension

Gastrointestinal disorders	dyspepsia.	pseudomembranous colitis (abdominal cramps or pain, tenderness, severe, watery diarrhoea which may also be bloody, fever), melaena, taste changes. Pancreatitis, tongue discoloration
Hepatobiliary disorders		transient elevations in liver enzymes, hepatitis, cholestatic jaundice. Hepatic failure (which has rarely resulted in death) (see section4.4), hepatitis fulminant, hepatic necrosis
Skin and subcutaneous tissue disorders	rash, pruritus	erythema multiforme, steven's-Johnson syndrome, toxic epidermal necrolysis. photosensitivity reaction, Urticaria
Musculoskeletal and connective tissue disorders	arthralgia	
Renal and urinary disorders		interstitial nephritis, acute renal failure, vaginitis. Renal failure acute, nephritis interstitial

General disorders and administration site conditions	fatigue	chest pain, oedema, malaise, asthenia
Investigations	lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased	aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea_increased, blood creatinine increased, blood potassium abnormal Electrocardiogram QTprolonged (see section4.4)

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “**6.04 Adverse Drug Reaction Reporting Form**”, found online under SAHPRA’s publications:

<https://www.sahpra.org.za/Publications/Index/8>

4.9 Overdose

Symptoms of overdose:

There is no data on overdosage of **AZITHROMYCIN AUSTELL**. Typical symptoms are expected to be those associated with macrolide antibiotics and include severe gastrointestinal symptoms (nausea, vomiting and diarrhoea) and hearing loss.

Treatment

In the event of overdose, the administration of medicinal charcoal and general symptomatic treatment and supportive measures are indicated as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A20.1.1 Broad and medium spectrum antibiotics.

Pharmacotherapeutic group: Antibacterials for systemic use; macrolides; azithromycin,

ATC Code: J01FA10

Mechanism of action

Azithromycin is a macrolide (azalide) antibiotic. It exerts its antibacterial action by binding reversibly to the 50S ribosomal subunit of the 70S ribosome of sensitive microorganisms, thereby inhibiting bacterial RNA-dependent protein synthesis. The *in vitro* antibacterial spectrum of pathogens sensitive to azithromycin includes:

(*in vitro* sensitivity does not necessarily imply *in vivo* efficacy)

Staphylococcus aureus

Streptococcus spp., including *Streptococcus pyogenes* (Group A) and

Streptococcus pneumoniae

Haemophilus influenzae, *Haemophilus ducreyi*

Moraxella catarrhalis

Legionella pneumophila

5.2 Pharmacokinetic properties

Absorption

Azithromycin is absorbed rapidly from the gastrointestinal tract, with an oral bioavailability of approximately 37 %. No significant decrease in bioavailability occurs when azithromycin is administered with a meal. Peak concentration occurs approximately 2 to 3 hours after oral administration.

Distribution

Protein binding of azithromycin is low (51 %) and appears to be concentration dependent, decreasing with increasing concentrations. Azithromycin is widely distributed throughout the body and concentrates intracellularly.

Biotransformation

Azithromycin (35 % of the dose) is metabolised by the liver to inactive metabolites and excreted in the bile.

Elimination

More than 50 % of the dose is eliminated unchanged via the bile, while 6,5 % of the dose is eliminated in the urine, unchanged. The elimination half-life of azithromycin closely reflects the tissue depletion half-life of 2 to 4 days.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Azithromycin dihydrate

Pregelatinised Starch

Crospovidone

Anhydrous calcium hydrogen phosphate

Sodium lauryl sulfate

Magnesium stearate

Hydroxypropyl methyl cellulose

Titanium dioxide

Lactose monohydrate

Glyceryl triacetate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

Keep blisters in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

White PVC, light resistant opaque, foil, heat sealed to aluminium foil, containing 2 or 3 tablets per pack, in an outer cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Camox Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown,

Johannesburg 2193

South Africa.

8. REGISTRATION NUMBER

A39/20.1.1/0020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 23 September 2005

10. DATE OF REVISION OF THE TEXT