Approved Professional Information for Medicines for Human Use:

AUSTELL AZITHROMYCIN 200 mg/5 ml

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

AUSTELL AZITHROMYCIN 200 mg/5 ml powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AUSTELL AZITHROMYCIN 200 mg/5 ml powder for oral suspension is a dry blend of azithromycin dihydrate and other excipients which when reconstituted with water, as directed, yields a suspension containing azithromycin dihydrate equivalent to 200 mg azithromycin per 5 mL.

AUSTELL AZITHROMYCIN 200 mg/ 5 ml contains sugar (sucrose: 3,87 g per 5 mL.

3. PHARMACEUTICAL FORM

AUSTELL AZITHROMYCIN 200 mg/5 ml powder for oral suspension

Before reconstitution: fine, off-white powder with banana-strawberry odour.

After reconstitution: a whitish liquid with banana-strawberry odour and flavour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Children: 1 year and older (under 45 kg)

AUSTELL AZITHROMYCIN 200 mg/5ml is indicated for the treatment of

pharyngitis/tonsillitis and otitis media caused by susceptible organisms.

Adults and children over 45 kg

AUSTELL AZITHROMYCIN 200 mg/5ml is indicated for mild to moderate infections caused by susceptible organisms; in lower respiratory tract infections including bronchitis due to *Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae or Staphylococcus aureus* and pneumonia due to *Streptococcus pneumoniae* or *Haemophilus influenzae*; uncomplicated skin and soft tissue infections; sinusitis due to *Haemophilus influenzae, Streptococcus pneumoniae* or *Staphylococcus aureus;* and as an alternative to first line therapy of pharyngitis/tonsillitis.

4.2 Posology and method of administration

Posology

AUSTELL AZITHROMYCIN 200 mg/5 ml powder for oral suspension should be administered as a single daily dose.

AUSTELL AZITHROMYCIN 200 mg/5 ml suspension should be administered to children using the 5 mL oral dosing syringe or the spoon provided.
AUSTELL AZITHROMYCIN 200 mg/5 ml suspension can be taken with food.

Paediatric population

Use in children: 1 year and older

The total dose in children is 30 mg/kg which should be given as a single daily dose of 10 mg/kg for 3 days according to the following guidance:

Weight	Dosage
< 15 kg	10 mg/kg once daily on days 1 - 3
15 - 25 kg	200 mg (5 mL) once daily on days 1 - 3
26 – 35 kg	300 mg (7,5 mL) once daily on days 1 - 3
36 – 45 kg	400 mg (10 mL) once daily on days 1 – 3
> 45 kg:	Dose as per adults (refer to AUSTELL AZITHROMYCIN 500 mg Tablets PI).

Method of administration

AUSTELL AZITHROMYCIN 200 mg/5 ml is for oral administration only.

See reconstitution of suspension in section 6.6.

4.3 Contraindications

- Hypersensitivity to azithromycin, erythromycin, or to any of the macrolide antibiotics or to any of the excipients listed in section 6.1.
- Because of the theoretical possibility of ergotism, AUSTELL AZITHROMYCIN 200 mg/5 ml and ergot derivatives should not be co-administered.
- Use in hepatic impairment: As the liver is the principal route of excretion of AUSTELL AZITHROMYCIN 200 mg/5 ml, it should not be used in patients with hepatic disease.
- Use during pregnancy and lactation: The safety and efficacy of AUSTELL AZITHROMYCIN 200 mg/5 ml in pregnancy and lactation have not been established.

4.4 Special warnings and precautions for use

Hypersensitivity

As with erythromycin and other macrolides, serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal), Acute Generalized Exanthematous Pustulosis (AGEP) 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.

Hepatoxicity

Cases of fulminant hepatitis potentially leading to life-threatening liver with azithromycin (see section 4.8).

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 ergot and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administrated.

Prolongation of the QT interval

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac dysrhythmia 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 substance known to prolong the QT interval such as antiarrhythmics of Classes Ia and III, cisapride and terfenadine
- with electrolyte disturbance, particularly in case of hypokalaemia and hypomagnesemia,
- 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 is recommended.

Clostridium difficile associated diarrhoea

Clostridium difficile associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial medicine, including azithromycin, and may range in severity from mild diarrhoea to fatal colitis. Strains of *C.difficile* producing hypertoxin 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 2 months after the administration of antibacterial medicines. 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/tonsilitis 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), 33 % increase in the systemic exposure to azithromycin was observed (see section 5.2).

Myesthenia 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).

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).

Diabetes

Caution in diabetic patients: 5 mL of reconstituted suspension contains 3,87 g of sucrose

Paediatric population

- Safety and efficacy in children under 1 year of age have not been established.
- Following the use of azithromycin, such as AUSTELL AZITHROMYCIN 200 mg/5 ml, in neonates (treatment up to 42 days of life), infantile hypertrophic pyloric stenosis (IHPS) has been reported. Parents and caregivers should be instructed to contact their doctor if vomiting or irritability with feeding occurs.

Excipient sucrose

This medicine contains sucrose: patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Antacids

AUSTELL AZITHROMYCIN 200 mg/5 ml should be taken at least 1 hour before or 2 hours after the antacid. In a pharmacokinetic study investigation the effects of simultaneous administration of antacid with azithromycin, no effect on overall bioavailability was seen, although peak serum concentrations were reduced. In patients receiving both azithromycin and antacids, the medicines should not be taken simultaneously.

Cetirizine

In healthy volunteer, co-administration 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)*

Co-administration of 1 200 mg/day azithromycin with 400 mg/day didanosine in six HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared to 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 1 000 mg doses and multiple 1 200 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 medicine 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 derivative 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

Co-administration 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 co-administration 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 who 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 AUC $_{0-\infty}$ were found to be significantly elevated, however no significant changes were seen in AUC $_{0-\infty}$. Consequently, caution should be exercised before considering concurrent administration of these medicines. If co-administration of these medicines is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

Efavirenz

Co-administration 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

Co-administration of a single dose of 1 200 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 co-administration of fluconazole, however, a clinically insignificant decrease in C_{max} of azithromycin was observed.

Indinavir

Co-administration of a single dose of 1 200 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.

Midazolam

In healthy volunteers, co-administration of 500 mg/day azithromycin for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single dose of 15 mg midazolam.

Nelfinavir

Co-administration 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

Co-administration of azithromycin and rifabutin did not affect the serum concentrations of either medicine. 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 3 days) on the AUC and Cmax, 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 healthy volunteers, co-administration of 500 mg azithromycin 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

Co-administration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days with 1 200 mg azithromycin 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 or 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 undertaken before prescribing azithromycin for any patients taking chloroquine, because of the potential for a similar risk with chloroquine.

4.6 Fertility, pregnancy and lactation

Safety and efficacy in pregnancy and lactation has not been established.

Pregnancy

Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. In these studies, no evidence of harm to the foetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women.

Breast-feeding

Limited information available from published literature indicates that azithromycin is present in human milk at an estimated highest median daily dose of 0,1 to 0,7 mg/kg/day. No serious adverse effects of azithromycin on the breast-fed infants were observed. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy.

4.7 Effects on ability to drive and use machines

Side effects dizziness, visual impairment, deafness have been reported with uses of AUSTELL AZITHRIOMYCIN 200 mg/5 ml. These side effects may affect a patient’s ability to drive or operate machinery.

4.8 Undesirable effects

AUSTELL AZITHROMYCIN 200 mg/ 5 ml is well tolerated with a low incidence of side effects.

The table below shows all adverse drug reactions (ADRs) observed during reported clinical trials and post-market spontaneous reports with Azithromycin dihydrate. Adverse reactions identified from post-marketing experience are included in italics.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Infections and infestations		Candidiasis, oral candidiasis, vaginal infection.	*Pseudomembranous colitis* (see section 4.4)
Blood and lymphatic system disorders		Neutropenia, leukopenia.	*Thrombocytopenia, haemolytic anaemia*
Immune system disorders		Angioedema, hypersensitivity.	*Anaphylactic reaction* (see section 4.4)

Metabolism and nutrition disorders	Anorexia.		
Psychiatric disorders		Nervousness, agitation.	*Aggression, anxiety*
Nervous system disorders	Dizziness, headache, paraesthesia, dysgeusia.	Hypoaesthesia, insomnia, somnolence	*Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis* (see section 4.4)
Eye disorders	Visual impairment.		
Ear and labyrinth disorders	Deafness.	Impaired hearing, tinnitus, vertigo.	
Cardiac disorders	Palpitations		*Torsades de pointes* (see section 4.4), dysrhythmia (see section 4.4) including *ventricular tachycardia*.
Vascular disorders			Hypotension.

Gastrointestinal disorders	Diarrhoea, abdominal pain, nausea, flatulence, vomiting, dyspepsia	Gastritis, constipation,	*Pancreatitis, tongue discoloration*
Hepatobiliary disorders		Hepatitis, hepatic function abnormal	*Hepatic failure* (see section 4.4) which has rarely resulted in death, *hepatitis fulminant, hepatic necrosis*, *jaundice cholestatic*
Skin and subcutaneous tissue disorders	Pruritus, rash.	Stevens Johnson syndrome (SJS), photosensitivity reaction, urticaria, acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS).	*Toxic epidermal necrolysis (TEN), erythema multiforme*

Musculoskeletal and connective tissue disorders	Arthralgia.		
Renal and urinary disorders			*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 QT prolonged* (see section 4.4)

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

Signs and symptoms

Symptoms:

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea.

Treatment

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A20.1.1 Broad and medium spectrum antibiotics

Pharmacotherapeutic group: Antibacterials for systemic use

ATC Code: J01FA10

Mechanism of action

Azithromycin is an azalide macrolide antibiotic. It exerts its antibacterial action by binding reversibly to the 50S ribosomal subunit of sensitive microorganisms, thereby inhibiting bacterial RNA-dependent protein synthesis.

In vitro sensitivity does not necessarily imply *in vivo* efficacy.

Azithromycin demonstrates activity *in vitro* against a wide range of Gram-positive

and Gram-negative bacteria including: *Staphylococcus aureus; Streptococcus pneumoniae, Streptococcus pyogenes* (Group A) and other Streptococcus species; *Haemophilus influenzae; Moraxella catarrhalis; Bordetella pertussis; Borrelia burgdorferi; Haemophilus ducreyi; and Chlamydia trachomatis*. Azithromycin also demonstrates *in vitro* activity against *Mycoplasma pneumoniae* and *Treponema pallidum.*

5.2 Pharmacokinetic properties

Absorption

Bioavailability is approximately 37 %. The time taken to peak plasma levels is 2 - 3 hours after oral administration.

Distribution

Azithromycin is widely distributed throughout the body Kinetic studies of variable times ranging from hours to days after oral intake have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the drug is highly tissue bound. Concentrations in target tissues such as lung, tonsil and prostate exceed the MIC90 for likely pathogens after a single dose of 500 mg.

Elimination

Most of the dose is eliminated unchanged via the bile, while approximately 12 % of the dose is eliminated in the urine, unchanged.

Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

banana flavour

hydroxypropylcellulose,

strawberry flavour,

sucrose,

trisodium phosphate (anhydrous),

xanthan gum,

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store in the original packaging until required for use.

Powder and reconstituted suspension should be stored at or below 25 °C.

Refrigeration is not required.

Discard unused suspension after 10 days.

After reconstitution: shake the bottle well before each dose.

Keep bottle tightly closed.

6.5 Nature and contents of container

AUSTELL AZITHROMYCIN 200 mg/ 5 ml is available in transparent amber glass bottles (Type III), with a polyethylene sealing disc and a white polyethylene cap in pack sizes of 15 and 30 mL. The bottles are further packed into cardboard boxes together with a dosing syringe.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Reconstituting instructions for AUSTELL AZITHROMYCIN 200 mg/5 ml powder for oral suspension for 15 mL and 30 mL bottles**:**

The table below indicates the volume of water to be used for constitution:

Amount of water to be added	Total deliverable volume	Azithromycin concentration after reconstitution
9 mL	15 mL (600 mg)	200 mg/5 mL
15 mL	30 mL (1200 mg)	200 mg/mL

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktowns

JOHANNESBURG, 2193

South Africa

Tel: +27 11 611 1400 or +27 860 287 835

8. REGISTRATION NUMBER

50/20.1.1/0567

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 March 2019

10. DATE OF REVISION OF THE TEXT

09 October 2023