Approved Professional Information for Medicines for Human Use:

VARIMAX

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

VARIMAX 250 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VARIMAX 250 mg capsule

Each capsule contains azithromycin dihydrate equivalent to 250 mg azithromycin base.

Methylparaben 0,14 % *m/m* (preservative).

Propylparaben 0,04 % *m/m* (preservative).

Contains sugar: lactose 144,90 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules.

Brown/white coloured, size ‘0”, hard gelatin capsules containing a white to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults and children over 45 kg:

VARIMAX is indicated for :

- mild to moderately severe 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;*

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- uncomplicated skin and soft tissue infections~~;~~
- sinusitis due to *Haemophilus influenzae, Streptococcus pneumoniae* or *Staphylococcus aureus*
- acute otitis media and pharyngitis/tonsillitis caused by susceptible organisms in children.

In sexually transmitted diseases in men and women, VARIMAX is indicated in the treatment of uncomplicated genital infections due to *Chlamydia trachomatis.*

4.2 Posology and method of administration

Posology

VARIMAX should be administered as a single daily dose at least 1 hour before or 2 hours after food.

Adults:

For all indications other than sexually transmitted diseases:

- the total dose is 1,5 g which should be given as 500 mg (2 capsules) daily for 3 days or alternatively an initial single oral dose of 500 mg on day 1, then 250 mg as a single daily dose for 4 days.

For sexually transmitted diseases caused by Chlamydia trachomatis:

- the dose is 1 g given as a single dose.

Special populations

Elderly population

Normal adult dosage is recommended.

Paediatric population

Children over 45 kg - dose as per adults.

This formulation is not suitable for children under 45 kg.

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Method of administration

VARIMAX is for oral administration.

4.3 Contraindications

- Hypersensitivity to azithromycin, erythromycin or any of the macrolide antibiotics.
- Because of the theoretical possibility of ergotism, VARIMAX and ergot derivatives should not be co- administered.
- Hepatic impairment: since biliary excretion is the principal route of excretion of VARIMAX.
- Pregnancy and lactation: The safety of VARIMAX in pregnancy and lactation have not been established (see section 4.6).

4.4 Special warnings and precautions for use

Hypersensitivity

Less frequent 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.

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 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 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 substance known to prolong 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

Pseudomembranous colitis or 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 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 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 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 inpatients 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).

Paediatric population

Use in children under 1 year of age:

The safety and efficacy of VARIMAX in children less than 1 year have not been established.

Excipient lactose

This medicine contains lactose:

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

Excipient sodium

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

4.5 Interaction with other medicines and other forms of interaction

Antacids:

In a pharmacokinetic study investigating the effects of simultaneous administration of antacid with azithromycin, no effect on overall bioavailability was seen, although peak serum concentrations were reduced by approximately 24%.

In patients receiving VARIMAX and antacids, VARIMAX should be taken at least 1 hour before or 2 hours after the antacid.

Cimetidine: A single dose of cimetidine administered 2 hours before VARIMAX had no effect on the pharmacokinetics of azithromycin.

Cetirizine:

In healthy volunteers, 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 1200 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 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 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:

Because of the theoretical possibility of ergotism, VARIMAX and ergot derivatives should not be co-administered (see section 4.4).

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).

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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.

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.

Cyclosporin:

Some of the related macrolide antibiotics interfere with the metabolism of cyclosporin. 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 cyclosporin, the resulting cyclosporin C_{max} and AUC_{0-5} were found to be significantly elevated (by 24 % and 21 % respectively), however no significant changes were seen in $AUC_{0-\infty}$. Consequently, caution should be exercised before co-administration of these two medicines. If co-administration is necessary, cyclosporin 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} (18 %) of azithromycin was observed.

Indinavir:

Co-administration 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.

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 (1 200 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 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, co-administration of 500mg 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 200mg 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.

Medicinal products which are known to prolong the QT interval (see section 4.4):

Azithromycin should be used with caution in patients receiving medicines known to prolong the QT interval with potential to induce cardiac arrhythmia, e.g. hydroxychloroquine.

4.6 Fertility, pregnancy and lactation

Pregnancy and breastfeeding:

The safety and efficacy of VARIMAX in pregnancy and lactation have not been established.

VARIMAX is contra-indicated during pregnancy and breastfeeding (see section 4.3).

Fertility

No fertility on data is available.

4.7 Effects on ability to drive and use machines

There is no evidence to suggest that VARIMAX may have an effect on a patient's ability to drive or operate machinery.

However, the possibility of undesirable effects like dizziness, somnolence, fatigue, and convulsions should be considered when performing these activities (see section 4.8).

Patients are therefore advised not to drive or use machinery or engage in other activities requiring mental alertness and coordination until they have established how VARIMAX affects them.

4.8 Undesirable effects

a) Summary of the safety profile

Varimax is well tolerated with a low incidence of side effects.

b) Tabulated list of adverse reactions

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

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Infections and infestations		Candidiasis, oral candidiasis, vaginitis	Pseudomembranous colitis
Blood and lymphatic system disorders		Leukopenia, neutropenia	Thrombocytopenia, haemolytic anaemia
Immune system disorders		Angioedema, hypersensitivity	Anaphylactic reaction
Metabolism and nutrition disorders	Anorexia		
Psychiatric disorders		Nervousness, agitation	Aggression, anxiety
Nervous system disorders	Dizziness, headache, paraesthesia, dysgeusia	Hypoaesethesia, somnolence, insomnia	Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia,

			myasthenia gravis
Eye disorders	Visual impairment		
Ear and labyrinth disorders	Deafness	Hearing impaired, tinnitus, vertigo	
Cardiac disorders		Palpitations, chest pain	Torsades de pointes, arrhythmia including ventricular tachycardia
Vascular disorders			Hypotension
Gastrointestinal disorders	Diarrhoea, loose stools, melaena, abdominal discomfort (pain/cramps), nausea, flatulence, vomiting, dyspepsia	Gastritis, constipation	Pancreatitis, tongue discolouration
Hepatobiliary disorders		Hepatitis, hepatic function abnormal, elevations in liver enzymes (elevated liver transaminases and bilirubin values).	Hepatic failure which has rarely resulted in death, hepatitis fulminant, hepatic necrosis, jaundice cholestatic
Skin and subcutaneous tissue disorders	Pruritus and rash	Steven's- Johnson syndrome, photosensitivity reaction, urticarial, Acute Generalized Exanthematous	Toxic epidermal necrolysis (TEN), erythema multiforme

		Pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS)	
Musculoskeletal and connective tissue disorders	Arthralgia		
Renal and urinary disorders			Renal failure acute, nephritis interstitial
General disorders and administration site conditions	Fatigue		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

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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

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

4.9 Overdose

Adverse events experienced in higher than recommended doses were similar to those seen in normal doses. Typical symptoms of overdosage with macrolide antibiotics include hearing loss, severe nausea, vomiting and diarrhoea. In the event of overdose, the administration of medicinal charcoal and general symptomatic treatment and general supportive measures are indicated as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 20.1.1 Broad and medium spectrum antibiotics.

Pharmacotherapeutic group: Antibacterials for systemic use.

ATC Code: J01FA10

Mechanism of action

Azithromycin is a macrolide antibiotic with bactericidal activity. These agents inhibit protein synthesis by binding reversibly to 50 S ribosomal subunits of sensitive micro-organisms.

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; Campylobacter spp., Pasteurella multocisa, L. pneumophila, Fusobacterium spp; Haemophilus ducreyi*; and *Chlamydia trachomatis*.

Azithromycin is also active against the protozoan *Toxoplasma gondii*, enterobacteriaceae such as *Escherichia coli, Salmonella* and Shigella spp and *Staphylococcus aureus, Chlamydia tragomatis* and S*. epidermis*.

VARIMAX also demonstrates in vitro activity against Mycoplasma pneumoniae and Treponema pallidum.

In vitro activity does not necessarily imply in vivo efficacy.

5.2 Pharmacokinetic properties

Absorption:

Following oral administration in humans, VARIMAX is absorbed rapidly. Bioavailability is approximately 37 %. The time taken to peak plasma levels is 2 - 3 hours after the initial dose. The bioavailability of azithromycin is significantly reduced by food.

Distribution:

VARIMAX is widely distributed throughout the body, except the cerebrospinal fluid.
Kinetic studies of variable times ranging from hours to days after oral intake have shown markedly higher VARIMAX levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the medicine 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:

Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. Only 6 % is excreted unchanged in the urine. The major route of elimination is through biliary excretion.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous lactose

Maize starch (dried)

Magnesium stearate

Colloidal anhydrous silica

Sodium lauryl sulphate

Gelatine Capsule:

Iron oxide (red)

Titanium dioxide

Methylparaben

Propylparaben

Sodium lauryl sulphate

Water

Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

VARIMAX 250 mg capsule: Blister packs (composed of transparent PVC and aluminium foil backing) of 3 or 6 capsules in a carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

36/20.1.1/0164

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 September 2003

10. DATE OF REVISION OF THE TEXT

19 April 2024