Proposed Clean Professional Information

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE

Azithromycin 500 Biotech, 500 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Azithromycin 500 Biotech: Each tablet contains azithromycin dihydrate equivalent to 500 mg azithromycin base.

Excipient(s) with known effect: 14,4 mg lactose monohydrate per film-coated tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

White to off-white, oval film-coated tablet with a breaking notch on one side. One-sided embossment "A500".

Azithromycin 500 Biotech tablets should be taken whole.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults: Azithromycin 500 Biotech is indicated for mild to moderate infections caused by susceptible organisms; in lower respiratory tract infections including bronchitis due to *Haemophilus influenza, 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. Azithromycin 500 Biotech is indicated in the

treatment of uncomplicated genital infections due to *Chlamydia trachomatis*, in sexually transmitted diseases in men and women.

Children: 1 year and over

Azithromycin 500 Biotech tablets are indicated for pharyngitis/tonsillitis and otitis media caused by susceptible organisms in children over 45 kg. (In children under 45 kg, an azithromycin suspension is recommended).

4.2 Posology and method of administration

Posology

Azithromycin 500 Biotech should be administered as a single dose with or without food.

Azithromycin 500 Biotech tablets should be taken whole.

Adults:

For all indications other than sexually transmitted diseases, the total dose is 1,5 g which should be given as 500 mg daily for 3 days.

Paediatrics:

Children over 45 kg – dose as per adults.

This formulation is not suitable for children under 45 kg.

Elderly:

Normal adult dosage is recommended.

4.3 Contraindications

Azithromycin 500 Biotech is contraindicated in patients with a known hypersensitivity to azithromycin, erythromycin or any of the macrolide antibiotics or to any excipient listed in section 6.1.

Because of the theoretical possibility of ergotism, Azithromycin 500 Biotech and ergot derivatives should not be co-administered.

Use in hepatic impairment:

Azithromycin 500 Biotech should not be used in patients with hepatic disease because the liver is the principal route of excretion of Azithromycin 500 Biotech.

Use during pregnancy and lactation:

The safety and efficacy of Azithromycin 500 Biotech in pregnancy and lactation have not been established.

4.4 Special warnings and precautions for use

Hypersensitivity:

Rare, serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), dermatologic reactions including Stevens Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) have been reported. Some of these reactions with Azithromycin 500 Biotech have resulted in recurrent symptoms and required a longer period of observation and treatment.

Fatalities have been reported. Cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have also been reported. Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further Azithromycin 500 Biotech exposure. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of Azithromycin 500 Biotech and subsequent prolonged exposure to antigen is presently unknown.

If an allergic reaction occurs, Azithromycin 500 Biotech should be discontinued, and appropriate therapy should be instituted. Medical practitioners should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

Hepatic impairment:

Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Discontinue Azithromycin 500 Biotech immediately if signs and symptoms of hepatitis occur.

Infantile Hypertrophic Pyloric Stenosis (IHPS)

IHPS has been reported in neonates (with treatment up to 42 days of life). Direct parents and caregivers to contact their medical practitioner if vomiting or irritability with feeding occurs.

Clostridium difficile-Associated Diarrhoea (CDAD):

Clostridium difficile associated diarrhoea (CDAD) also called pseudomembranous colitis has been reported with use of nearly all antibacterial agents, including Azithromycin 500 Biotech, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which 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. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. In case of CDAD anti-peristaltics are contraindicated.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Renal impairment:

In patients with severe renal impairment (GFR < 10 ml/min) a 33 % increase in systemic exposure to Azithromycin 500 Biotech was observed.

Cardiovascular events

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, including Azithromycin 500 Biotech (refer to section 4.8). Cases of torsades de pointes have been spontaneously reported during post marketing surveillance in patients. Providers should consider the risk of QT prolongation which can be fatal when

weighing the risks and benefits of Azithromycin 500 Biotech for at-risk groups including:

- Patients with known prolongation of the QT interval, a history of torsades de pointes, congenital long QT syndrome, bradydysrhythmias or uncompensated heart failure.
- Patients on drugs known to prolong the QT interval.
- Patients with ongoing prodysrhythmic conditions such as uncorrected hypokalaemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antidysrhythmic agents.

Elderly patients may be more susceptible to drug-associated effects on the QT interval.

Myasthenia gravis

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving Azithromycin 500 Biotech therapy (refer to section 4.8).

Development of Drug-Resistant Bacteria

Prescribing Azithromycin 500 Biotech in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Paediatric population:

The safety and efficacy for the prevention or treatment of *Mycobacterium avium* complex in children have not been established.

The following should be considered before prescribing Azithromycin 500 Biotech:

Azithromycin 500 Biotech is not suitable for treatment of severe infections where a high concentration of the antibiotic in the blood is rapidly needed.

The selection of Azithromycin 500 Biotech to treat an individual patient should take into account the appropriateness of using a macrolide antibacterial agent based on adequate diagnosis to ascertain the

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bacterial aetiology of the infection in the approved indications and the prevalence of resistance to Azithromycin 500 Biotech or other macrolides.

In areas with a high incidence of erythromycin A resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to Azithromycin 500 Biotech and other antibiotics.

As for other macrolides, high resistance rates of *Streptococcus pneumonia* (> 30 %) have been reported. This should be taken into account when treating infections caused by *Streptococcus pneumoniae*.

Pharyngitis/ tonsillitis

Azithromycin 500 Biotech is not the substance of first choice for the treatment of pharyngitis and tonsillitis caused by *Streptococcus pyogenes*. For this and for the prophylaxis of acute rheumatic fever penicillin is the treatment of first choice.

Sinusitis

Often, Azithromycin 500 Biotech is not the substance of first choice for the treatment of sinusitis

Acute otitis media

Often, Azithromycin 500 Biotech is not the substance of first choice for the treatment of acute otitis media.

Skin and soft tissue infections

The main causative agent of soft tissue infections, *Staphylococcus aureus*, is frequently resistant to Azithromycin 500 Biotech. Therefore, susceptibility testing is considered a precondition for treatment of soft tissue infections with Azithromycin 500 Biotech.

Infected burn wounds:

Azithromycin 500 Biotech is not indicated for the treatment of infected burn wounds.

Sexually transmitted disease:

In case of sexually transmitted diseases a concomitant infection by *T. pallidium* should be excluded.

Azithromycin 500 Biotech, at the recommended dose, should not be relied upon to treat *T.pallidium.* Antibacterial agents used to treat non-gonococcal urethritis may mask or delay the symptoms of incubating *T.pallidium.* All patients with sexually transmitted urethritis or cervicitis should have a serologic test for *T.pallidium* and appropriate testing for gonorrhoea performed at the time of diagnosis. Appropriate antibacterial therapy and follow-up tests for these diseases should be initiated if infection is confirmed.

Neurological or psychiatric diseases:

Azithromycin 500 Biotech should be used with caution in patients with neurological or psychiatric disorders.

Sodium

Azithromycin 500 Biotech contains less than 1 mmol (23 mg) of sodium per tablet, that is to say it is essentially 'sodium-free.'

Azithromycin 500 Biotech contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take Azithromycin 500 Biotech.

4.5 Interaction with other medicines and other forms of interaction

Ergot derivatives:

In a pharmacokinetic study investigating the effects of simultaneous administration of antacids with azithromycin, no effect on overall bioavailability was seen, although peak serum levels were reduced by approximately 25 %. Azithromycin 500 Biotech and ergot derivatives should not be co-administered because of the theoretical possibility of ergotism (refer to section 4.4).

Special administration advised with the following:

Antacids:

In a pharmacokinetic study investigating the effects of simultaneous administration of antacids with Azithromycin 500 Biotech, no effect on overall bioavailability was seen, although peak serum levels were reduced by approximately 25 %. In patients receiving Azithromycin 500 Biotech and antacids, the medicines should not be taken simultaneously. Azithromycin 500 Biotech should be taken at least 1 hour before or 2 hours after the antacid.

Cimetidine:

A single dose of cimetidine administered 2 hours before Azithromycin 500 Biotech had no effect on the pharmacokinetics of Azithromycin 500 Biotech.

No interactions reported with the following:

Carbamazepine:

No significant effect was observed on the plasma levels of carbamazepine or its active metabolite, in a pharmacokinetic interaction study in healthy volunteers.

Methylprednisolone:

In a pharmacokinetic interaction study in healthy volunteers, Azithromycin 500 Biotech had no significant effect on the pharmacokinetics of methylprednisolone.

Theophylline:

There is no evidence of any pharmacokinetic interaction when Azithromycin 500 Biotech and theophylline are co-administered to healthy volunteers.

Zidovudine:

Single 1000 mg doses of Azithromycin 500 Biotech had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of Azithromycin 500 Biotech 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 500 Biotech 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 500 Biotech.

Cetirizine:

In healthy volunteers, coadministration of a 5-day regimen of Azithromycin 500 Biotech with cetirizine 20 mg 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.

Efavirenz:

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

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.

Midazolam:

In healthy volunteers, coadministration of Azithromycin 500 Biotech for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single 15 mg dose of midazolam.

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.

Sildenafil:

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

Triazolam:

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In 14 healthy volunteers, coadministration of Azithromycin 500 Biotech 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.

Special precautionary monitoring is advised with the following:

Cyclosporin:

In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of Azithromycin 500 Biotech 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. Consequently, caution should be exercised before considering concurrent administration of these medicines. If coadministration of these medicines is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Digoxin (P-gp substrates) and colchicine:

Concomitant administration of macrolide antibiotics, including Azithromycin 500 Biotech, 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 500 Biotech and P-gp substrates such as digoxin are administered concomitantly, the possibility of elevated serum concentrations of the substrate should be considered.

Phenytoin

Interactions with phenytoin has not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interactions. However, drug interactions have been observed with other macrolide products. Until further data are developed regarding drug interactions when phenytoin is used concomitantly with azithromycin careful monitoring of patients is

advised.

Warfarin:

In a pharmacokinetic interaction study, Azithromycin 500 Biotech did not alter the anticoagulant effect of a single 15 mg dose of warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to coadministration of Azithromycin 500 Biotech and coumarin type oral anticoagulants. Azithromycin 500 Biotech and warfarin may be co-administered but monitoring of the prothrombin time should be continued as routinely performed.

Terfenadine:

Pharmacokinetic studies have reported no evidence of an interaction between Azithromycin 500 Biotech and terfenadine. There have been less frequent reported of an interaction in patients receiving Azithromycin 500 Biotech and terfenadine where the possibility of such an interaction could not entirely be excluded.

Astemizole, alfentanil:

There are no known data on interactions with astemizole or alfentanil. Caution is advised in the co-administration of these medicines with Azithromycin 500 Biotech because of the known enhancing effect of these medicines when used concurrently with the macrolide antibiotic erythromycin.

Atorvastatin:

Coadministration of atorvastatin (10 mg daily) and Azithromycin 500 Biotech (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on an HMG CoA-reductase inhibition assay). However, post-marketing cases of rhabdomyolysis in patients receiving Azithromycin 500 Biotech with statins have been reported.

Cisapride:

Cisapride is metabolized in the liver by the enzyme CYP 3A4. Because macrolides inhibit this enzyme, concomitant administration of cisapride may cause the increase of QT interval prolongation, ventricular dysrhythmias and torsades de pointes.

Nelfinavir:

Co-administration of nelfinavir at steady-state with a single oral dose of Azithromycin 500 Biotech resulted in increased Azithromycin 500 Biotech serum concentrations. Although a dose adjustment of Azithromycin

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500 Biotech is not recommended when administered in combination with nelfinavir, close monitoring for known adverse reactions of Azithromycin 500 Biotech, such as liver enzyme abnormalities and hearing impairment, is warranted (refer to section 4.8).

Rifabutin:

Coadministration of Azithromycin 500 Biotech and rifabutin did not affect the serum concentrations of either medicines. Neutropenia was observed in subjects receiving concomitant treatment of Azithromycin 500 Biotech and rifabutin.

Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with Azithromycin 500 Biotech has not been established (refer to section 4.8).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of Azithromycin 500 Biotech in pregnant women. In reproduction toxicity studies in animals Azithromycin 500 Biotech was shown to pass the placenta, but no teratogenic effects were observed. The safety of Azithromycin 500 Biotech has not been confirmed with regard to the use of the active substance during pregnancy.

Breastfeeding

Azithromycin 500 Biotech has been reported to be secreted into human breastmilk, but there are no adequate and well controlled clinical studies in nursing women that have characterized the pharmacokinetics of Azithromycin 500 Biotech excretion into human breastmilk.

Because it is not known whether Azithromycin 500 Biotech may have adverse effects on the breastfed infant, nursing should be discontinued during treatment with Azithromycin 500 Biotech. Among other things diarrhoea, fungus infection of the mucous membrane as well as sensitisation is possible in the nursed infant. It is recommended to discard the milk during treatment and up until 2 days after discontinuation of treatment. Nursing may be resumed thereafter.

Fertility

In fertility studies conducted in rats, reduced pregnancy rates were noted following administration of

Azithromycin 500 Biotech. The relevance of this finding to humans is unknown.

4.7 Effects on ability to drive and use machines

No data are available regarding the influence of Azithromycin 500 Biotech 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. Visual impairment and vision blurred may have an effect on a patient's ability to drive or operate machinery (refer to section 4.8).

4.8 Undesirable effects

Tabulated summary of adverse reactions

Infections and infestations	
Less frequent:	Moniliasis
Blood and lymphatic system disorders	
Less frequent:	Leukopenia, thrombocytopenia*, neutropenia
Immune system disorders	
Less frequent:	Angioedema, anaphylactic reaction (refer to section 4.4.)
Metabolism and nutrition disorders	
Frequent:	Anorexia
Psychiatric disorders	
Less frequent:	Nervousness*, aggression reaction*, agitation*, anxiety*
Nervous system disorders	
Frequent:	Headache, dizziness, dysgeusia, paraesthesia, somnolence
Frequency not known:	Syncope*, convulsion, hyperactivity*, anosmia*
Eye disorders	
Less frequent:	Abnormal vision
Ear and labyrinth disorders	

Frequent:	Deafness
Less frequent:	Vertigo, hearing impaired including hearing loss*, tinnitus
Cardiac disorders	
Less frequent:	Palpitations, chest pain, dysrhythmia (refer to section 4.4) including ventricular tachycardia, electro-cardiogram QT prolonged* (refer to section 4.4), Torsades de pointes* (refer to section 4.4)
Vascular disorders	
Less frequent:	Hypotension*
Gastrointestinal disorders	
Frequent:	Diarrhoea (rarely resulting in dehydration), abdominal discomfort (pain/cramps), nausea, and vomiting (less frequently resulting in dehydration)
Less frequent:	Constipation, dyspepsia, flatulence, loose stools, melaena
Frequency not known:	Pseudomembranous colitis*, pancreatitis*, tongue discoloration*, oral candidiasis*, pyloric stenosis*
Hepatobiliary disorders	
Less frequent:	Hepatitis, hepatic function abnormal*, cholestatic jaundice, hepatic necrosis* and hepatic failure* (which has rarely resulted in death)
Skin and subcutaneous tissue disorders	
Less frequent:	Pruritus, rash, photosensitivity reaction, urticaria, serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis* and erythema multiforme*
Frequency not known:	DRESS (Drug reaction with eosinophilia and systemic symptoms)*

Musculoskeletal and connective tissue disorders	
Frequent:	Arthralgia
Renal and urinary disorders	
Less frequent:	Acute renal failure, interstitial nephritis, nephritis
Reproductive system and breast disorders	
Less frequent:	Vaginitis
General disorders and administration site conditions	
Frequent:	Fatigue
Less frequent:	Oedema, asthenia, malaise*

*Post-marketing side effects

Paediatric population

The types of adverse reactions in paediatric patients were comparable to those seen in adults, with different incidence rates for the dosage regimens recommended in paediatric patients.

Blood and lymphatic disorders	
Less frequent:	Anaemia and leukopenia
Immune system disorders	
Less frequent:	Allergic reaction
Nervous system disorders	
Frequent:	Headache
Less frequent:	Hyperkinesia, dizziness, agitation, nervousness, and insomnia
Eye disorders	
Less frequent:	Conjunctivitis
Cardiac disorders	
Less frequent:	Chest pain
Respiratory, thoracic and mediastinal disorders	

Less frequent:	Cough, pharyngitis, pleural effusion, and rhinitis
Gastrointestinal disorders	
Frequent:	Diarrhoea, abdominal pain, vomiting, nausea
Less frequent:	Dyspepsia, constipation, anorexia, enteritis, flatulence, gastritis, jaundice, loose stools, and oral moniliasis
Skin and subcutaneous tissue disorders	
Frequent:	Rash
Less frequent:	Eczema, fungal dermatitis, pruritus, sweating, urticaria, and vesiculobullous rash
General disorders and administration site conditions	
Less frequent:	Fever, face oedema, fatigue, fungal infection, malaise, and pain

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 providers 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

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses.

Symptoms

Typical symptoms of overdosage with macrolide antibiotics include hearing loss, severe nausea, vomiting and diarrhoea.

Treatment

Gastric lavage and general symptomatic and supportive measures are indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, macrolides. ATC code: J01FA10.

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:

Azithromycin 500 Biotech is widely distributed throughout the body following oral administration; bioavailability is approximately 37 %. No significant decrease in bioavailability was observed when azithromycin tablets were administered with food. The time taken to peak plasma levels is 2 - 3 hours.

Distribution:

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) thus showing that azithromycin is highly bound in tissue.

After a single dose of 500 mg, concentrations in target tissue such as the lung, tonsil and prostate exceed the MIC90 for likely pathogens.

Elimination:

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

Specific Populations:

Renal Insufficiency:

Azithromycin pharmacokinetics was investigated in 42 adults (21 to 85 years of age) with varying degrees of renal impairment. Following the oral administration of a single 1,0 g dose of azithromycin, mean C_{max} and AUC_{0-120} increased by 5,1 % and 4,2 %, respectively, in subjects with mild to moderate renal impairment (GFR 10 to 80 ml/min) compared to subjects with normal renal function (GFR > 80 ml/min). The mean C_{max} and AUC_{0-120} increased 61 % and 35 %, respectively, in subjects with severe renal impairment (GFR < 10 ml/min) compared to subjects with normal renal function (GFR > 80 ml/min).

Hepatic Insufficiency:

The pharmacokinetics of azithromycin in subjects with hepatic impairment has not been established.

Geriatric Patients:

Pharmacokinetic parameters in older volunteers (65 to 85 years old) were similar to those in young adults (18 to 40 years old) for the 5-day therapeutic regimen. Dosage adjustment does not appear to be necessary for older patients with normal renal and hepatic function receiving treatment with this dosage regimen.

Paediatric Patients:

In two clinical studies, azithromycin for oral suspension was dosed at 10 mg/kg on day 1, followed by 5 mg/kg on days 2 through 5 in two groups of paediatric patients (aged 1 - 5 years and 5 - 15 years, respectively). The mean pharmacokinetic parameters on day 5 were C_{max} = 0,216 mcg/ml, T_{max} = 1,9 hr, and AUC_{0-24} = 1,822 mcg·hr/ml for the 1 to 5-year-old group and were C_{max} = 0,383 mcg/ml, T_{max} = 2,4 hr, and AUC_{0-24} = 3,109 mcg·hr/ml for the 5 to 15-year-old group.

In another study, 33 paediatric patients received doses of 12 mg/kg/day (maximum daily dose 500 mg) for 5 days, of whom 31 patients were evaluated for azithromycin pharmacokinetics following a low-fat breakfast. In this study, azithromycin concentrations were determined over a 24-hr period following the last daily dose. Patients weighing above 41,7 kg received the maximum adult daily dose of 500 mg. Seventeen patients (weighing 41,7 kg or less) received a total dose of 60 mg/kg. The following table shows pharmacokinetic data in the subset of paediatric patients who received a total dose of 60 mg/kg.

Pharmacokinetic Parameter [mean (SD)]	5-Day Regimen (12 mg/kg for 5 days)

N	17
C_{max} (mcg/mL)	0,5 (0,4)
T_{max} (hr)	2,2 (0,8)
AUC_{0-24} (mcg.hr/mL)	3,9 (1,9)

Single dose pharmacokinetics of azithromycin in paediatric patients given doses of 30 mg/kg have not been studied.

5.3 Preclinical safety data

In animal studies using exposures 40 times those achieved at the clinical therapeutic dosages, azithromycin was found to have caused reversible phospholipidosis, but as a rule there were no associated toxicological consequences. The relevance of this finding to humans receiving azithromycin in accordance with the recommendations is unknown.

Electrophysiological investigations have shown that azithromycin prolongs the QT interval.

Carcinogenic potential:

Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Mutagenic potential:

There was no evidence of a potential for genetic and chromosome mutations in *in-vivo* and *in-vitro* test models.

Reproductive toxicity:

Teratogenic effects were not observed in rat reproductive toxicity studies. In rats, azithromycin doses of 100 and 200 mg/kg body weight/ day led to mild retardation in foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats mild retardations in physical and reflex development were noted following treatment with 50 mg/kg/day azithromycin and above.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

magnesium stearate

maize starch

microcrystalline cellulose

silica colloidal anhydrous

sodium lauryl sulphate

sodium starch glycollate

Coating (Opadry white):

hydroxypropyl methylcellulose

lactose monohydrate

macrogol 4000

purified water

titanium dioxide

6.2 Incompatibilities

None

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Do not remove the blisters form the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Azithromycin 500 Biotech are packed into white, opaque PVC/ Aluminium blisters of 2, 3 or 10 tablets

each.

6.6 Special precautions for disposal and other handling

None.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd.

Ground Floor,

Bock K West, Central Park

400, 16th Road, Randjespark

Midrand, 1685

8. REGISTRATION NUMBER(S)

A39/20.1.1/0382

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09 December 2008

10. DATE OF REVISION OF THE TEXT

24 November 2019