Professional information for AZITHROMYCIN BIOTECH S

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

AZITHROMYCIN BIOTECH S 200 mg/5 mL powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL of AZITHROMYCIN BIOTECH S contains 200 mg azithromycin (as dihydrate).

Excipients with known effect:

Contains sugar (3,87 g sucrose per 5 mL).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension.

Fine off-white powder with banana-strawberry flavour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Children: 1 year and over (under 45 kg):

AZITHROMYCIN BIOTECH S is indicated for pharyngitis/tonsillitis and otitis media caused by susceptible organisms.

***Adults and children over 45 kg*:**

AZITHROMYCIN BIOTECH S 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:

AZITHROMYCIN BIOTECH S should be administered as a single daily dose.

AZITHROMYCIN BIOTECH S should be administered to children using the 5 mL oral dosing syringe provided.

AZITHROMYCIN BIOTECH S 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:

< 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 on days 1 – 3.

36 – 45 kg: (400 mg) 10 mL once on days 1 – 3.

> 45 kg: dose as per adults (refer to the professional information of AZITHROMYCIN BIOTECH 500 tablets).

Method of administration:

AZITHROMYCIN BIOTECH S is for oral administration only.

For instructions on reconstitution of the product before administration, see section 6.6.

4.3 Contraindications

- AZITHROMYCIN BIOTECH S is contraindicated in patients with a known hypersensitivity to azithromycin, erythromycin, any of the macrolide antibiotics, or to any excipient listed under section 6.1.
- Because of the theoretical possibility of ergotism, AZITHROMYCIN BIOTECH S and ergot derivatives should not be co-administered.
- Use in hepatic impairment: As the liver is the principal route of excretion of AZITHROMYCIN BIOTECH S, it should not be prescribed in patients with hepatic disease.
- Use in children under 1 year of age: The safety and efficacy of AZITHROMYCIN BIOTECH S in children under 1 year of age have not been established.
- Use during pregnancy and lactation: The safety and efficacy of AZITHROMYCIN BIOTECH S in pregnancy and lactation have not been established.

4.4 Special warnings and precautions for use

Hypersensitivity

Serious allergic reactions, including angioedema, anaphylaxis and dermatologic reactions including Stevens- Johnson syndrome, acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis have been reported. Some of these reactions with azithromycin, as in AZITHROMYCIN BIOTECH S, have resulted in recurrent symptoms and required a longer period of observation and treatment (see section 4.3).

If an allergic reaction occurs, AZITHROMYCIN BIOTECH S should be discontinued, and appropriate therapy should be instituted. Medical practitioners to 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 BIOTECH S should be undertaken with caution in patients with hepatic disease (see section 4.8).

Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis and hepatic failure, some of which have resulted in death, have been reported. Discontinue AZITHROMYCIN BIOTECH S immediately if signs and/or symptoms of hepatitis occur.

Infantile hypertrophic pyloric stenosis (IHPS)

Following the use of azithromycin in neonates (treatment up to 42 days of life), infantile hypertrophic pyloric stenosis (IHPS) has been reported. Parents and caregivers should be informed to contact their health care provider if vomiting or irritability with feeding occurs.

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 BIOTECH S. However, because of the theoretical possibility of ergotism, AZITHROMYCIN BIOTECH S and ergot derivatives should not be co-administered (see section 4.3).

Superinfection

Observation for signs of superinfection with non-susceptible organisms, including fungi, is recommended.

Pseudomembranous colitis

Pseudomembranous colitis has been reported and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients with diarrhoea subsequent to administration of AZITHROMYCIN BIOTECH S.

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.

If CDAD is suspected or confirmed, ongoing AZITHROMYCIN BIOTECH S use should be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *Clostridium difficile,* and surgical evaluation should be instituted as clinically indicated.

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 (GRF < 10 mL /min), a 33 % increase in systemic exposure to azithromycin was observed (see section 5.2). Acute renal failure and interstitial nephritis have been reported (see section 4.8).

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 including AZITHROMYCIN BIOTECH S (see section 4.8).

Prescribers should specifically consider the risk of QT prolongation, which can be fatal in at-risk groups including:

- Patients with congenital or documented QT prolongation.
- Patients currently receiving treatment with other medicines known to prolong QT interval,

such as antidysrhythmics of Classes IA (quinidine and procainamide) and III (dofetilide, amiodarone and sotalol), cisapride and terfenadine, antipsychotic medicines such as pimozide, antidepressants such as citalopram and fluoroquinolones such as moxifloxacin and levofloxacin.

- Patients with electrolyte disturbance, particularly in case of hypokalaemia and hypomagnesaemia.
- Patients with clinically relevant bradycardia, cardiac dysrhythmia or cardiac insufficiency.
- Elderly patients: elderly patients may be more susceptible to medicine-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, as in AZITHROMYCIN BIOTECH S (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

- The safety and efficacy of AZITHROMYCIN BIOTECH S in children less than 1 year have not been established.
- Following the use of azithromycin, such as AZITHROMYCIN BIOTECH S, 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.

Sucrose warning

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take AZITHROMYCIN BIOTECH S.

4.5 Interaction with other medicines and other forms of interaction

Ergot derivatives

Because of the theoretical possibility of ergotism, AZITHROMYCIN BIOTECH S and ergot derivatives should not be co-administered (see sections 4.3 and 4.4).

Cetirizine

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

Azithromycin does not interact significantly with the hepatic cytochrome P450 system. It is not believed to be associated with the pharmacokinetic medicine interactions seen with erythromycin. Hepatic cytochrome P450 induction or inactivation via cytochrome-metabolite complex does not occur with azithromycin.

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). However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin with statins

have been reported.

Efavirenz

Co-administration 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.

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 1 200 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, co-administration of azithromycin 500 mg/day for 3 days did not cause clinically significant changes in the pharmacokinetic properties and pharmacodynamic properties of a single 15 mg dose of 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 although a dose adjustment of AZITHROMYCIN BIOTECH S is not recommended when administered in combination with nelfinavir, close monitoring for known side effects of AZITHROMYCIN BIOTECH S is warranted.

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 C_{max} of sildenafil or its major circulating metabolite.

Triazolam

In healthy volunteers, co-administration 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

Co-administration of trimethoprim/sulfamethoxazole (160 mg/800 mg) for 7 days with azithromycin 1 200 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 administration advised with the following:

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 BIOTECH S and antacids, the medicines should not be taken simultaneously. AZITHROMYCIN BIOTECH S should be taken at least 1 hour before or 2 hours after an antacid.

Cimetidine

A single dose of cimetidine administered 2 hours before AZITHROMYCIN BIOTECH S had no effect on the pharmacokinetics of AZITHROMYCIN BIOTECH S.

No pharmacokinetic interactions were reported in studies of AZITHROMYCIN BIOTECH S

co-administered with:

Carbamazepine, methylprednisolone, didanosine (dideoxyinosine), theophylline, rifabutin

however co-administration of AZITHROMYCIN BIOTECH S and rifabutin was associated with the development of neutropenia. A causal relationship to its combination with AZITHROMYCIN BIOTECH S has not been established (see section 4.8)) and *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).

Special precautionary monitoring is advised with the following:

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 AUC_{0-5} were found to be significantly elevated (C_{max} increase by 24 % and AUC_{0-5} was 5 107 and 4 210 ngh/mL with and without azithromycin, respectively, $p \leq 0,05$). Consequently, caution should be exercised before co-administration of these two medicines. If co-administration is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

P-glycoprotein substrates

Concomitant administration of AZITHROMYCIN BIOTECH S with P-glycoprotein substrates such as digoxin or dabigatran has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if AZITHROMYCIN BIOTECH S and P-glycoprotein substrates such as digoxin or dabigatran are administered concomitantly, the possibility of elevated serum medicine concentrations should be considered. Clinical monitoring and serum monitoring of digoxin levels during treatment with AZITHROMYCIN BIOTECH S and after its discontinuation are necessary.

Some of the macrolide antibiotics have been reported to impair the metabolism of digoxin (in the gut) in some patients. Therefore, in patients receiving concomitant AZITHROMYCIN BIOTECH S, a related azalide antibiotic, and digoxin the possibility of raised digoxin levels should be borne in mind.

Warfarin

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

Medicines 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

The safety and efficacy of AZITHROMYCIN BIOTECH S in pregnancy and lactation have 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. Because animal reproduction studies are not always predictive of human response, AZITHROMYCIN BIOTECH S should be used during pregnancy only if clearly needed.

Breastfeeding

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 breastfed infants were observed. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from azithromycin therapy.

4.7 Effects on ability to drive and use machines

Side effects such as dizziness, convulsions, vertigo, somnolence, and syncope have been reported with usage of AZITHROMYCIN BIOTECH S. These side effects may affect a patient's ability to performing tasks requiring attention.

4.8 Undesirable effects

The following undesirable effects have been reported:

System organ class	**Frequency**	**Side effects**
Infections and Infestations	*Less frequent*	candidiasis, vaginal infection, pneumonia, fungal infection, bacterial infection, pharyngitis, gastroenteritis, respiratory disorder, rhinitis, oral candidiasis
	Frequency unknown	pseudomembranous colitis (see section 4.4)
	Less frequent	leukopenia, neutropenia, eosinophilia

Blood and lymphatic system disorders	*Frequency unknown*	thrombocytopenia, haemolytic anaemia
Immune system disorders	*Less frequent*	angioedema, hypersensitivity
	Frequency unknown	anaphylactic reaction (see section 4.4)
Metabolism and nutrition disorders	*Frequent*	anorexia
Psychiatric disorders	*Less frequent*	nervousness, insomnia, agitation
	Frequency unknown	aggression, anxiety, delirium, hallucinations
Nervous system disorders	*Frequent*	headache, dizziness, dysgeusia, paraesthesia
	Less frequent	somnolence, insomnia, hypoesthesia
	Frequency unknown	syncope, convulsions, psychomotor hyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis (see section 4.4)
Eye disorders	*Frequent*	visual impairment
	Frequency unknown	blurred vision
Ear and labyrinth disorders	*Frequent*	deafness
	Less frequent	ear disorder, vertigo, hearing impairment, tinnitus
Cardiac disorders	*Less frequent*	palpitations
	Frequency unknown	torsades de pointes (see section 4.4), dysrhythmia (see section 4.4) including ventricular tachycardia, prolonged electrocardiogram QT (see section 4.4)
Vascular disorders	*Less frequent*	hot flushes

	Frequency unknown	hypotension
Respiratory, thoracic and mediastinal disorders	*Less frequent*	dyspnoea, epistaxis
Gastrointestinal disorders	*Frequent*	diarrhoea, vomiting, abdominal pain, nausea, flatulence, dyspepsia
	Less frequent	constipation, gastritis dysphagia, abdominal distension, dry mouth, eructation, mouth ulceration, salivary hypersecretion
	Frequency unknown	pancreatitis, tongue discolouration
Hepatobiliary disorders	*Less frequent*	hepatitis, abnormal hepatic function, cholestatic jaundice
	Frequency unknown	hepatic failure (which has rarely resulted in death) (see section 4.4), hepatitis fulminant, hepatic necrosis
Skin and subcutaneous tissue disorders	*Frequent*	Rash, pruritus
	Less frequent	Stevens-Johnson syndrome, urticaria, dermatitis, dry skin, hyperhidrosis, photosensitivity reaction, acute generalised exanthematous pustulosis (AGEP)
	Frequency unknown	toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders	*Frequent*	arthralgia
	Less frequent	osteoarthritis, myalgia, back pain, neck pain
	Less frequent	dysuria, renal pain

Renal and urinary disorders		
	Frequency unknown	acute renal failure, interstitial nephritis
Reproductive system and breast disorders	*Less frequent*	metrorrhagia, testicular disorder
General disorders and administration site conditions	*Frequent*	fatigue
	Less frequent	oedema, asthenia, malaise, face oedema, chest pain, pyrexia, pain, peripheral oedema
Investigations	*Frequent*	decreased lymphocyte count, increased eosinophil count, decreased blood bicarbonate, increased basophils, increased monocytes, increased neutrophils
	Less frequent	increased aspartate aminotransferase, increased alanine aminotransferase, increased blood bilirubin, increased blood urea, increased blood creatinine, abnormal blood potassium, increased blood alkaline phosphatase, increased chloride, increased glucose, increased platelets, decreased hematocrit, increased bicarbonate, abnormal sodium
	Frequency unknown	electrocardiogram QT prolonged (see section 4.4)
Injury and poisoning	*Less frequent*	post procedural complication.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of AZITHROMYCIN BIOTECH S is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care

providers are requested to report any suspected adverse reactions to the South African Health Products Regulatory Authority (SAHPRA) via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class:

A 20.1.1 Broad and medium spectrum antibiotics

Pharmacotherapeutic groups and ATC code:

Antibacterials for systemic use, J01FA10

Azithromycin is an azalide, a subclass of the macrolide antibiotics. Chemically it is derived by insertion of a nitrogen atom into the lactone ring of erythromycin A. The chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin A. The molecular weight is 749,0 g/mol.

Azithromycin binds to the 23S rRNA of the 50S ribosomal subunit. It blocks protein synthesis by inhibiting the transpeptidation/ translocation step of protein synthesis and by inhibiting the assembly of the 50S ribosomal subunit.

Cardiac electrophysiology:

QTc interval-prolongation was studied in a randomised, placebo-controlled parallel trial in 116

healthy subjects who received either chloroquine (1 000 mg) alone or in combination with azithromycin (500 mg, 1 000 mg, and 1 500 mg once daily). Co-administration of azithromycin significantly increased the QTc interval in a dose- and concentration-dependent manner. In comparison to chloroquine alone, the maximum mean (95 % upper confidence bound) increases in QTcF were 5 (10) ms, 7 (12) ms and 9 (14) ms with the co-administration of 500 mg, 1 000 mg and 1 500 mg azithromycin, respectively.

Efflux pumps occur in a number of bacteria, including Gram-negatives, such as *Haemophilus influenzae* (where they may determine intrinsically higher MICs) and staphylococci. In streptococci and enterococci, an efflux pump that recognises 14- and 15-membered macrolides (which include, respectively, erythromycin and azithromycin) is encoded by *mef*(A) genes.
Azithromycin demonstrates cross-resistance with erythromycin- resistant Gram-positive organisms. Ribosomal modifications determine cross-resistance with other classes of antibiotics whose ribosomal binding sites overlap that of the macrolides: the lincosamides (including clindamycin), and the streptogramins B (which include, for example, the quinupristin component of quinupristin/dalfopristin). A decrease in macrolide susceptibility over time has been noted in particular in *Streptococcus pneumoniae* and *Staphylococcus aureus* and has also been observed in *viridans streptococci* and in *Streptococcus agalactiae*.

Azithromycin has *in vitro* activity against:

- Aerobic and facultative Gram-positive bacteria (erythromycin-susceptible organisms).
- Aerobic and facultative Gram-negative bacteria.

In vitro resistance to azithromycin:
Azithromycin-resistant organisms are encountered relatively frequently among aerobic and facultative Gram-positive bacteria, in particular among methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin- resistant *Streptococcus pneumoniae* (PRSP).
Pseudomonas spp. and most *Enterobacteriaceae* are inherently resistant to azithromycin, although azithromycin has been used to treat *Salmonella enterica, Pneumocystis jirovecii* and *Toxoplasma*

gondii infections.

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

5.2 Pharmacokinetic properties

Absorption

Following oral administration in humans, azithromycin is widely distributed throughout the body; bioavailability is approximately 37 %. No significant decrease in bioavailability was observed when azithromycin was administered with a meal. The time taken to peak plasma levels is 2 to 3 hours.

In patients hospitalised with community acquired pneumonia receiving single daily one-hour intravenous infusions for 2 to 5 days of 500 mg azithromycin at a concentration of 2 mg/mL, the mean C_{max} ± S.D. achieved was 3,63 ± 1,60 µg/mL, while the 24-hour trough level was 0,20 ± 0,15 µg/mL, and the AUC_{24} was 9,60 ± 4,80 µg·h/mL.

The mean C_{max}, 24-hour trough and AUC_{24} values were 1,14 ± 0,14 µg/L; 0,18 ± 0,02 µg/mL and 8,03 ± 0,86 µg·h/mL, respectively, in normal volunteers receiving a 3-hour intravenous infusion of 500 mg azithromycin at a concentration of 1 mg/mL.

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) indicating that the medicine is highly tissue bound. Concentrations in target tissues such as lung, tonsils and prostate gland 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. Approximately 12 % of an intravenously administered dose is excreted in the urine over 3 days as

azithromycin, the majority in the first 24 hours. Biliary excretion of azithromycin is a major route of elimination for unchanged medicine following oral administration. Very high concentrations of unchanged medicine have been found in human bile together with 10 metabolites, formed through *N*- and *O*-demethylation, by hydroxylation of desosamine and aglycone rings, and by cleavage of the cladinose conjugate. Comparison of HPLC and microbiological assays in tissues suggests that metabolites play no part in the microbiological activity of azithromycin.

In a multiple-dose study in 12 normal volunteers utilising a 500 mg (1 mg/mL) one-hour intravenous-dosage regimen for five days, the amount of administered azithromycin dose excreted in urine in 24 hours was about 11 % after the 1st dose and 14 % after the 5th dose. These values are greater than the reported 6 % excreted unchanged in urine after oral administration of azithromycin.

Pharmacokinetics in special patient groups:

Renal impairment:

The pharmacokinetics of azithromycin in adult patients with mild-to-moderate renal impairment (GFR 10 – 80 mL/min) were not affected following a single 1 g dose of immediate release azithromycin. Statistically significant differences in AUC_{0-120} (8,8 mg × hr/mL vs. 11,7 mg × hr/mL), C_{max} (1,0 mg/mL vs. 1,6 mg/mL) and CLr (2,3 mL/min/kg vs. 0,2 mL/min/kg) were observed between the group with severe renal impairment (GFR < 10 mL/min) and the group with normal renal function.

Hepatic impairment:

In patients with mild (Class A) to moderate (Class B) hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to those with normal hepatic function. The urinary clearance of azithromycin appears to increase in these patients, perhaps to compensate for reduced hepatic clearance. Azithromycin has not been studied and should not be used in patients with severe hepatic impairment.

Elderly:

Elderly volunteers (> 65 years) had slightly higher AUC values than in young volunteers (< 40 years) after a 5-day regimen, but these are not considered clinically significant, and hence no dose adjustment is recommended.

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Banana flavour

Hydroxypropylcellulose

Strawberry flavour

Sucrose

Trisodium phosphate (anhydrous)

Xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Before reconstitution:

5 years.

Store at or below 25 °C.

After reconstitution:

10 days.

Store at or below 25 °C.

6.4 Special precautions for storage

AZITHROMYCIN BIOTECH S does not require any special storage conditions.

6.5 Nature and contents of container

Transparent, clean, type III amber glass bottle without noticeable defects with a white, polyethylene cap with a polyethylene sealing disc. A syringe with a white plastic seal is included as an administration device. The bottle and syringe are packed into an outer carboard carton.

Pack sizes: 15 mL and 30 mL.

6.6 Special precautions for disposal and other handling

Reconstitution instructions for AZITHROMYCIN BIOTECH S* 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 content)	Azithromycin concentration after reconstitution
9 mL	15 mL (600 mg)	200 mg/5 mL
15 mL	30 mL (1 200 mg)	200 mg/5 mL

Shake well before each use.

Oversized bottle provides shake space. Keep tightly closed.

Appearance after reconstitution:

Whitish liquid with banana-strawberry flavour.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground floor, Block K West, Central park

400 16th Road, Randjespark

Midrand 1685

Tel no: 011 848 3050

8. REGISTRATION NUMBER

49/20.1.1/1032

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 May 2021

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30 June 2026