Professional Information for Medicines for Human Use

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ZATYP ORAL SUSPENSION (powder for oral suspension)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZATYP ORAL SUSPENSION (powder for oral suspension):

Each teaspoonful (5 mL) contains azithromycin dihydrate equivalent to azithromycin 200 mg. Contains sugar (3887.95 mg sucrose).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off-white, granular powder, forming a pale to dark pink flavoured suspension when reconstituted with water.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Children: 1 year and over (under 45 kg)

ZATYP ORAL SUSPENSION is indicated for pharyngitis/tonsillitis and otitis media caused by susceptible organisms.

Adults and children over 45 kg:

ZATYP ORAL SUSPENSION 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

ZATYP ORAL SUSPENSION 200 mg/5 mL powder for oral suspension should be administered as a single daily dose.

ZATYP ORAL SUSPENSION should be administered to children using the 5 mL oral dosing syringe or the spoon provided ZATYP ORAL SUSPENSION suspension can be taken with food.

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 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 azithromycin 500 mg Tablets Professional Information)

Method of administration

For oral use.

For reconstitution details please refer to section 6.6

4.3. Contraindications

ZATYP ORAL SUSPENSION is contra-indicated in patients with a known hypersensitivity to azithromycin, erythromycin or any of the macrolide antibiotics, or to any excipients under section 6.1.

Because of the theoretical possibility of ergotism, ZATYP ORAL SUSPENSION and ergot derivatives should not be co-administered.

Use in hepatic impairment

As the liver is the principal route of excretion of ZATYP ORAL SUSPENSION, it should not be used in patients with hepatic disease.

Use in children under 1 year of age

The safety and efficacy of ZATYP ORAL SUSPENSION in children less than 1 year of age 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 Exanthemateous Pustulosis (AGEP), Drug with Eosinophilic and systemic symptoms (DRESS) and toxic epidermal necrolysis have been reported. Some of these reactions with ZATYP ORAL SUSPENSION have resulted in recurrent symptoms and required a longer period of observation and treatment

If an allergic reaction occurs, ZATYP ORAL SUSPENSION 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 ZATYP ORAL SUSPENSION should be undertaken with caution in patients with hepatic disease (see section 4.3).

Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure, some of which have resulted in death, have been reported. Discontinue ZATYP ORAL SUSPENSION immediately if signs and symptoms of hepatitis occur.
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 ZATYP ORAL SUSPENSION. However, because of the theoretical possibility of ergotism, [PRODUCT NAME] 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 ZATYP ORAL SUSPENSION.
***Clostridium difficile*-associated diarrhoea:** *Clostridium difficile*-associated diarrhoea (CDAD) due to overgrowth of *Clostridium difficile* in the gut, has been reported with use of ZATYP ORAL SUSPENSION, and may range in severity from mild diarrhoea to fatal colitis. If CDAD is suspected or confirmed, ongoing ZATYP ORAL SUSPENSION 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.
Renal impairment: In patients with a creatinine clearance < 30, a 33 % increase in systemic exposure to ZATYP ORAL

SUSPENSION was observed (see Section 5.2). Acute renal failure and interstitial nephritis have been reported (see Section 4.8).

QT Prolongation

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac dysrhythmia and Torsades de Pointes, have been seen with treatment with macrolides, including ZATYP ORAL SUSPENSION (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 active substances known to prolong QT interval such as antidysrhythmics of classes IA and III; antipsychotic agents; antidepressants; and fluoroquinolones
- Patients with electrolyte disturbance, particularly in cases 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

Exacerbation of symptoms of myasthenia gravis and new-onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy.

Use in children under 1 year of age:

The safety and efficacy of oral ZATYP ORAL SUSPENSION preparations in children less than 1 year have not been established

4.5. Interaction with other medicines and other forms of interaction:

Because of the theoretical possibility of ergotism, ZATYP ORAL SUSPENSION and ergot derivatives should not be co-administered (see Section 4.3 and Section 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 ZATYP ORAL SUSPENSION is not recommended when administered in combination with nelfinavir, close monitoring for known side effects of ZATYP ORAL SUSPENSION 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 14 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 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 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 ZATYP ORAL SUSPENSION and antacids, the medicines should not be taken simultaneously. ZATYP ORAL SUSPENSION should be taken at least 1 hour before or 2 hours after an antacid.

Cimetidine:

A single dose of cimetidine administered 2 hours before ZATYP ORAL SUSPENSION had no effect on the pharmacokinetics of ZATYP ORAL SUSPENSION.

No pharmacokinetic interactions were reported in studies of ZATYP ORAL SUSPENSION co-administered with:

Carbamazepine, methylprednisolone,didanosine (dideoxyinosine), theophylline, rifabutin however co-administration of ZATYP ORAL SUSPENSION and rifabutin was associated with the development of neutropenia. A causal relationship to its combination with ZATYP ORAL SUSPENSION 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 ZATYP ORAL SUSPENSION 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 ZATYP ORAL SUSPENSION 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 ZATYP ORAL SUSPENSION 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 ZATYP ORAL SUSPENSION, 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 15 mg dose of warfarin administered to healthy volunteers. However, there have been reports received in

the post-marketing period of potentiated anticoagulation subsequent to co-administered of azithromycin and warfarin. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when ZATYP ORAL SUSPENSION is used in patients receiving coumarin-type oral anticoagulants.

4.6. Fertility, pregnancy and lactation

The safety and efficacy of ZATYP ORAL SUSPENSION 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, ZATYP ORAL SUSPENSION should be used during pregnancy only if clearly needed.

Lactation:

Azithromycin has been reported to be secreted into human breast milk, but there are no adequate and well- controlled clinical studies in nursing women that have characterised the pharmacokinetics of azithromycin excretion into human breast milk.

ZATYP ORAL SUSPENSION should only be used in lactating women where adequate alternatives are not available.

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 ZATYP ORAL SUSPENSION. These side effects may affect a patient's ability to drive or operate machinery.

4.8. Undesirable effects

System organ class	Frequency	Side effects
Infections and Infestations	Less Frequent Unknown	Candidiasis, Vaginal infection, Pneumonia, Fungal infection, Bacterial infection, Pharyngitis, Gastroenteritis, Respiratory disorder, Rhinitis, Oral candidiasis. Pseudomembranous colitis (see section 4.4)
Blood and Lymphatic System Disorders	Less Frequent Unknown	Leukopenia, Neutropenia, Eosinophilia. Thrombocytopenia, Haemolytic anaemia
Immune System Disorders	Less Frequent Unknown	Angioedema, Hypersensitivity Anaphylactic reaction (see section 4.4)
Metabolism and Nutrition Disorders	Less Frequent	Anorexia
Psychiatric Disorders	Less Frequent Unknown	Nervousness, Insomnia, Agitation Aggression, Anxiety, Delirium, Hallucination

Nervous System Disorders	Frequent Less Frequent Unknown	Headache, Dizziness, Somnolence, Dysgeusia, Paraesthesia. Syncope, convulsion, hypoestheia, Psychomotor hyperactivity, Anosmia,
Eye Disorders	Unknown	Visual impairment, blurred vision
Ear and Labyrinth Disorders	Less Frequent Unknown	Ear disorder, Vertigo Hearing impairment including deafness and/or tinnitus
Skin and subcutaneous tissue disorders	Less Frequent Unknown	Rash, Pruritus, Urticaria, Dermatitis, Dry skin, Hyperhidrosis, Photosensitivity reaction, Acute generalised exanthematous pustulosis (AGEP). Stevens-Johnson syndrome, Toxic epidermal necrolysis, Erythema multiforme
Cardiac Disorders	Less Frequent Unknown	Palpitations Torsades de pointes (see section 4.4), Dysrhythmia (see section 4.4) including

		ventricular tachycardia, Electrocardiogram QT prolonged (see section 4.4)
Vascular Disorders	Less Frequent Unknown	Hot flush Hypotension
Respiratory, thoracic and mediastinal disorders	Less Frequent	Dyspnoea, Epistaxis
Gastrointestinal Disorders	Frequent Less Frequent Unknown	Diarrhoea, Vomiting, Abdominal pain, Nausea Constipation, Flatulence, Dyspepsia, Gastritis dysphagia, Abdominal distension, Dry mouth, Eructation, Mouth ulceration, Salivary hypersecretion Pancreatitis, Tongue discolouration
Hepatobiliary Disorders	Less Frequent Unknown	Hepatic function abnormal, Jaundice cholestatic Hepatic failure (which has rarely resulted in death) (see

		section 4.4), Hepatitis fulminant, Hepatic necrosis	
Musculoskeletal and Connective Tissue Disorders	Less Frequent Unknown	Osteoarthritis, Myalgia, Back pain, Neck pain Arthralgia	
Renal and urinary disorders	Less Frequent Unknown	Dysuria, Renal pain Renal failure acute, Nephritis interstitial	
Reproductive system and breast disorders	Less Frequent	Metrorrhagia, Testicular disorder	
General disorders and administration site conditions	Less Frequent	Oedema, Asthenia, Malaise, Fatigue, Face oedema, Chest pain, Pyrexia, Pain, Peripheral oedema	
Investigations	Frequent Less Frequent	Lymphocyte count decreased, Eosinophil count increased, Blood bicarbonate decreased, Basophils increased, Monocytes increased, Neutrophils increased Aspartate aminotransferase	

		increased, Alanine aminotransferase increased, Blood bilirubin increased, Blood urea increased, Blood creatinine increased, Blood potassium abnormal, Blood alkaline phosphatase increased, Chloride increased, Glucose increased platelets increased, Hematocrit decreased, Bicarbonate increased abnormal sodium.	
Injury and poisoning	Less Frequent	Post procedural complication	

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 provders are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse DrugReactions 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. Typical symptoms of overdosage with macrolide antibiotics include hearing loss, severe nausea, vomiting and diarrhoea. General supportive measures are indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use; macrolides; azithromycin ATC code: 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.
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

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 - 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, 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. 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 by N and O-demethylation, by hydroxylation of the 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

The other ingredients of ZATYP ORAL SUSPENSION are art cherry flavour, art ripe banana flavour, FD&C red No. 40, hydroxypropyl cellulose, sucrose (60/200), sucrose (200), tribasic sodium phosphate anhydrous and xanthan gum.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

2 years

6.4. Special precautions for storage

For dry powder: Store at or below 25 °C

For reconstitution suspension: The reconstitution suspension should be stored at or below 25 °C and any unused suspension should be discarded after 10 days. No refrigeration required.

Keep HDPE containers tightly closed.

KEEP OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container

White to off-white, granular powder, forming a pale to dark pink flavoured suspension on constituted with water.

HDPE bottle:

15 mL:

ZATYP ORAL SUSPENSION is a dry powder filled in 30 mL white opaque round heavy weight HDPE bottle closed with 28 mm white opaque polypropylene child resistant closure with peelable aluminium induction sealing liner.

(15 mL after reconstitution).

30 mL:

ZATYP ORAL SUSPENSION is a dry powder filled in 60 mL white opaque round heavy weight HDPE bottle closed with 28 mm white opaque polypropylene child resistant closure with peelable aluminium induction sealing liner

(30 mL after reconstitution).

The outer carton also contains a 10 ml plastic syringe with 0,2 mL graduation.

Pack size: 15 mL and 30 mL.

6.6. Special precautions for disposal and other handling of the product

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Reconstituting instructions for ZATYP ORAL SUSPENSION 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 content)	Azithromycin concentration after reconstitution
9 mL	15 mL (600 mg)	200 mg/5 mL
15 mL	30 mL (1200 mg)	200 mg/5 mL

Reconstituted suspension is a pale to dark pink suspension.

Shake well before each use. Oversized bottle provides shake space. Keep tightly closed.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

AUROGEN SOUTH AFRICA (Pty) Ltd

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Johannesburg

South Africa

8. REGISTRATION NUMBER

51/20.1.1/0269.267

9. DATE OF FIRST AUTHORISATION

28 July 2020

10. DATE OF REVISION OF TEXT

Not applicable