PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

Azrasite 200 mg/5 ml

Powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Azrasite 200 mg/5 ml powder for oral suspension is a dry blend of azithromycin dihydrate and other excipients which yields on reconstitution with water, a suspension containing the equivalent of 200 mg azithromycin per 5 ml.

Excipients: Sugar (sucrose): 3,9 g/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 odour

After reconstitution with water a white to off-white suspension is formed which has a banana-strawberry odour and taste

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Children 1 year and over (under 45 kg):

Azrasite 200 mg/5 ml indicated for pharyngitis/tonsillitis and otitis media caused by susceptible organisms.

Adults and children over 45 kg:

Azrasite 200 mg/5 ml 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

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

Posology

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

Azrasite 200mg/5 ml suspension should be administered to children using a 10 ml oral dosing syringe

Azrasite 200 mg/5 ml suspension can be taken with food.
Shake well before each use. Keep tightly closed. After mixing store below 25 °C (no refrigeration required) and discard any unused suspension after 5 days.

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:
Oral administration only

4.3 Contraindications

Azrasite 200 mg/5 ml 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, Azrasite 200 mg/5 ml and ergot derivatives should not be co- administered.

Use in hepatic impairment:

As the liver is the principal route of excretion of Azrasite 200 mg/5 ml, it should not be prescribed in patients with hepatic disease.

Use in children under 1 year of age:

The safety and efficacy of Azrasite 200 mg/5 ml have not been established

4.4 Special warnings and precautions for use

Hypersensitivity: Serious allergic reactions including angioedema and 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 Azrasite 200 mg/5 ml have resulted in recurrent symptoms and required a longer period of observation and treatment.
If an allergic reaction occurs, Azrasite 200 mg/5 ml 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, Azrasite 200 mg/5 ml 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 Azrasite 200 mg/5 ml immediately if signs and/or symptoms of hepatitis occur.

In case of signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests/ investigations should be performed immediately. Azrasite 200 mg/5 ml administration should be stopped if liver dysfunction has emerged

Ergot derivatives: In patients receiving ergot derivatives, ergotism has been precipitated by co-administration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergot and Azrasite 200 mg/5 ml. However, because of the theoretical possibility of ergotism, Azrasite 200 mg/5 ml 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 Azrasite 200 mg/5 ml.

***Clostridium difficile* associated diarrhoea (CDAD):** *Clostridium difficile*-associated diarrhoea (CDAD) due to overgrowth of *Clostridium difficile* in the gut, has been reported with use of Azrasite 200 mg/5 ml, and may range in severity from mild diarrhoea to fatal colitis.

If CDAD is suspected or confirmed, ongoing Azrasite 200 mg/5 ml 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 Azrasite 200 mg/5 ml 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 macrolide antibiotics including Azrasite 200 mg/5 ml (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: Exacerbations of the 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 Azrasite 200 mg/5 ml preparations in children less than 1 year have not been established.

Diabetes:

Caution in diabetic patients: 5 ml of reconstituted suspension contains 3.9 g of sucrose.

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

4.5 Interaction with other medicines and other forms of interaction

Ergot derivatives: Because of the theoretical possibility of ergotism, Azrasite 200 mg/5 ml 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 Azrasite 200 mg/5 ml is not recommended when administered in combination with nelfinavir, close monitoring for known side effects of Azrasite 200 mg/5 ml 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 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 Azrasite 200 mg/5 ml and antacids, the medicines should not be taken simultaneously. Azrasite 200 mg/5 ml should be taken at least 1 hour before or 2 hours after an antacid.

Administration of oral antacids is not expected to affect the disposition of azithromycin given intravenously.

Cimetidine:

A single dose of cimetidine administered 2 hours before Azrasite 200 mg/5 ml had no effect on the pharmacokinetics of Azrasite 200 mg/5 ml.

No pharmacokinetic interactions were reported in studies of Azrasite 200 mg/5 ml coadministered with:

Carbamazepine, methylprednisolone, didanosine (dideoxyinosine), theophylline, rifabutin however co-administration of Azrasite 200 mg/5 ml and rifabutin was associated with the development of neutropenia. A causal relationship to its combination with Azrasite 200 mg/5 ml 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 ng.h/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 Azrasite 200 mg/5 ml 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 Azrasite 200 mg/5 ml 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 Azrasite 200 mg/5 ml 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 Azrasite 200 mg/5 ml, 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 coadministration of azithromycin and warfarin. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when Azrasite 200 mg/5 ml is used in patients receiving coumarin-type oral anticoagulants.

4.6 Fertility, pregnancy and lactation

The safety and efficacy of Azrasite 200 mg/5 ml 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 should be used during pregnancy only if clearly needed.

Lactation:

Azithromycin has been reported to be excreted 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.

Azrasite 200 mg/5 ml 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 Azrasite 200 mg/5 ml. These side effects may affect a patient's ability to drive or operate machinery.

4.8 Undesirable effects

The following undesirable effects have been reported.

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)

Blood and Lymphatic System Disorders

Less Frequent - Leukopenia, Neutropenia, Eosinophilia.

Frequency unknown - Thrombocytopenia, Haemolytic anaemia

Immune System Disorders

Less Frequent - Angioedema, Hypersensitivity

Frequency unknown - Anaphylactic reaction (see section 4.4)

Metabolism and Nutrition Disorders

Less Frequent – Anorexia

Psychiatric Disorders

Less Frequent - Nervousness, Insomnia, Agitation

Frequency unknown - Aggression, Anxiety, Delirium, Hallucination

Nervous System Disorders

Frequent – Headache

Less Frequent - Dizziness, Somnolence, Dysgeusia, Paraesthesia.

Frequency unknown - Syncope, convulsion, Hypoestheia, Psychomotor hyperactivity, Anosmia, Myasthenia gravis

Eye Disorders

Frequency unknown – Visual impairment, Blurred vision

Ear and Labyrinth Disorders

Less Frequent - Ear disorder, Vertigo

Frequency unknown - Hearing impairment including deafness and/or tinnitus

Skin and subcutaneous tissue disorders

Less Frequent - Rash, Pruritus, Urticaria, Dermatitis, Dry skin, Hyperhidrosis, Photosensitivity reaction, Acute generalised exanthematous pustulosis (AGEP). Drug reaction with eosinophilia and systemic symptoms (DRESS).

Frequency unknown - Stevens-Johnson syndrome, Toxic epidermal necrolysis, Erythema multiforme

Cardiac Disorders

Less Frequent – Palpitations

Frequency unknown - 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 - Hot flush

Frequency unknown – Hypotension

Respiratory, thoracic and mediastinal disorders

Less Frequent - Dyspnoea, Epistaxis

Gastrointestinal Disorders

Frequent - Diarrhoea, Vomiting, Abdominal pain, Nausea

Less Frequent - Constipation, Flatulence, Dyspepsia, Gastritis dysphagia, abdominal distension, dry mouth, Eructation, Mouth ulceration, salivary hypersecretion

Frequency unknown - Pancreatitis, Tongue discolouration

Hepatobiliary Disorders

Less Frequent - Hepatic function abnormal, Jaundice cholestatic

Frequency unknown - Hepatic failure (which has rarely resulted in death) (see section 4.4), Hepatitis fulminant, Hepatic necrosis

Musculoskeletal and Connective Tissue Disorders

Less Frequent - Osteoarthritis, Myalgia, Back pain, Neck pain

Frequency unknown – Arthralgia

Renal and urinary disorders

Less Frequent - Dysuria, Renal pain

Frequency unknown - 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 - Lymphocyte count decreased, Eosinophil count increased, Blood bicarbonate decreased, Basophils increased, Monocytes increased, Neutrophils increased

Less Frequent - 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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdosage

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

5. PHARMACOLOGICAL ACTION

5.1 Pharmacodynamic properties

Antibacterials for systemic use. 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 lindamycin), 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 - 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. 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.

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

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trisodium phosphate

Sucrose

Hydroxypropylcellulose

Xanthan gum

Banana flavour

Strawberry flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Azrasite 200 mg/5 ml for oral suspension: 5 years

Once reconstituted with water, Azrasite 200 mg/5 a shelf life of 5 days at 25 ºC.

6.4 Special precautions for storage

Store at or below 25 °C. Shake bottle well before use. Keep tightly closed.

The reconstituted suspension should be stored below 25 °C and any unused portion should be discarded after 5 days.

6.5 Nature and contents of container

Transparent amber glass bottle (15 ml or 30 ml) with a white polyethylene cap containing an inner polyethylene disc. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution instructions for Azrasite 200 mg/5 ml powder for oral suspension for 15 ml and 30 ml bottles:

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

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

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

After mixing store below 25 °C (no refrigeration required) and discard any unused suspension after 5 days.

After reconstitution with water a white to off-white suspension is formed which has a banana-strawberry odour and taste

Medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ruby Pharmaceuticals (PTY) LTD

P.O. Box 431

Pinetown 3600

8. REGISTRATION NUMBER:

51/20.1.1/0554

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION:

27/10/2020

10. DATE OF REVISION OF THE TEXT: Not applicable