1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

AZITHROMYCIN S ASPEN 200 mg/5 ml, powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

On reconstitution with water, each 5 ml of AZITHROMYCIN S ASPEN contains azithromycin dihydrate equivalent to 200 mg of azithromycin.

Contains sugar: Sucrose 3,81 g

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension.

AZITHROMYCIN S ASPEN is off-white to cream coloured, free flowing granular powder/loose agglomerates (which are readily dispersible with simple tapping).

After reconstitution with water, AZITHROMYCIN S ASPEN is a white to off-white homogenous suspension with a slight strawberry/banana flavour and vanilla odour.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Children: 1 year and over (under 45 kg)

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

Adults and children over 45 kg:

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

AZITHROMYCIN S ASPEN suspension should be administered to children using a 5 ml oral dosing syringe or a medicine measure provided.

AZITHROMYCIN S ASPEN 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:

Weight	Dose
< 15 kg	10 mg/kg once daily on days 1 to 3
15 kg to 25 kg	200 mg (5 ml) once daily on days 1 to 3
26 kg to 35 kg	300 mg (7,5 ml) once daily on days 1 to 3
36 kg to 45 kg	400 mg (10 ml) once daily on days 1 to 3
> 45 kg	Dose as per adults with tablet formulation

Method of administration

For oral administration. AZITHROMYCIN S ASPEN should be administered as a single daily dose for 3 days. AZITHROMYCIN S ASPEN can be taken with food.

Shake well before use.

For reconstitution instructions see section 6.6.

4.3. Contraindications

AZITHROMYCIN S ASPEN is contraindicated in:

- Patients with hypersensitivity to azithromycin, erythromycin, any of the macrolide or ketolide antibiotics or to any excipients in AZITHROMYCIN S ASPEN (see section 6.1).
- Because of the theoretical possibility of ergotism, AZITHROMYCIN S ASPEN and ergot derivatives should not be co-administered.
- **Hepatic impairment:**

  As the liver is the principal route of excretion of AZITHROMYCIN S ASPEN, it should not be prescribed in patients with hepatic disease.

- **Use in children under 1 year of age:**

  The safety and efficacy of AZITHROMYCIN S ASPEN in children less than 1 year has 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 Reaction with Eosinophilic and systemic symptoms (DRESS) and toxic epidermal necrolysis have been reported. Some of these reactions with AZITHROMYCIN S ASPEN have resulted in recurrent symptoms and required a longer period of observation and treatment.

If an allergic reaction occurs, AZITHROMYCIN S ASPEN 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.

Hepatic impairment

Since the liver is the principal route of elimination for azithromycin, the use of AZITHROMYCIN S ASPEN should be undertaken with caution in patients with significant 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 AZITHROMYCIN S ASPEN immediately if signs and/or symptoms of hepatitis occur.

Ergot alkaloids

In patients receiving ergot derivatives, ergotism has been precipitated by coadministration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergotamine derivatives and azithromycin, as in AZITHROMYCIN S ASPEN. However, because of the theoretical possibility of ergotism, AZITHROMYCIN S ASPEN and ergot derivatives should not be co-administered (see section 4.3 and section 4.5).

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 macrolides including AZITHROMYCIN S ASPEN (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.

- Currently receiving treatment with other medicines known to prolong QT interval such as anti-dysrhythmic medicines of classes IA and III; antipsychotic medicines; antidepressants; and fluoroquinolones.
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia.
- With clinically relevant bradycardia, cardiac dysrhythmia or severe cardiac insufficiency.

Elderly patients: elderly patients may be more susceptible to medicine-associated effects on the QT interval.

Superinfections

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 S ASPEN.

Clostridium difficile associated diarrhoea

Clostridium difficile associated diarrhoea (CDAD) due to overgrowth of *Clostridium difficile* in the gut, has been reported with the use of nearly all antibacterial medicines, including azithromycin, as in AZITHROMYCIN S ASPEN, and may range in severity from mild diarrhoea to fatal colitis.

If CDAD is suspected or confirmed, ongoing AZITHROMYCIN S ASPEN 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 AZITHROMYCIN S ASPEN was observed (see section 5.2). Acute renal failure and interstitial nephritis have been reported (see section 4.8).

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 S ASPEN (see section 4.8).

Paediatric population

The safety and efficacy of AZITHROMYCIN S ASPEN has not been established in children less than 1 year of age.

Excipients

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

4.5. Interaction with other medicines and other forms of interaction

Ergot derivatives:

Because of the theoretical possibility of ergotism, AZITHROMYCIN S ASPEN 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 AZITHROMYCIN S ASPEN is not recommended when administered in combination with nelfinavir, close monitoring for known side effects of AZITHROMYCIN S ASPEN 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 AZITHROMYCIN S ASPEN and antacids, the medicines should not be taken simultaneously. AZITHROMYCIN S ASPEN 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 S ASPEN had no effect on the pharmacokinetics of AZITHROMYCIN S ASPEN.

No pharmacokinetic interactions were reported in studies

of AZITHROMYCIN S ASPEN co-administered with:

Carbamazepine, methylprednisolone, didanosine (dideoxyinosine), theophylline, rifabutin however co-administration of AZITHROMYCIN S ASPEN and rifabutin was associated with the development of neutropenia. A causal relationship to its combination with AZITHROMYCIN S ASPEN 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 S ASPEN 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 S ASPEN 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 S ASPEN 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 S ASPEN, 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-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 S ASPEN is used in patients receiving coumarin-type oral anticoagulants.

4.6. Fertility, pregnancy and lactation

The safety of AZITHROMYCIN S ASPEN in pregnancy and lactation has 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 S ASPEN should be used during pregnancy only if clearly needed.

Breastfeeding

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.

AZITHROMYCIN S ASPEN should only be used in lactating women where adequate alternatives are not available.

Fertility

There are no fertility data 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 AZITHROMYCIN S ASPEN. These side effects may affect a patient's ability to drive or operate machinery.

4.8. Undesirable effects

a. Tabulated list of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)

Infections and infestations		Candidiasis, oral candidiasis, vaginal infection, pneumonia, fungal infection, bacterial infection, pharyngitis, gastroenteritis, respiratory disorder, rhinitis	Pseudo-membranous colitis (see section 4.4)
Blood and the lymphatic system disorders		Leukopenia, neutropenia, eosinophilia	Thrombocytopenia, haemolytic anaemia
Immune system disorders		Angioedema, hypersensitivity	Anaphylactic reaction (see section 4.4)
Metabolism and nutrition disorders		Anorexia	
Psychiatric disorders		Nervousness, agitation, insomnia	Aggression, anxiety, delirium, hallucination
Nervous system disorders	Headache	Dizziness, dysgeusia, paraesthesia, somnolence	Syncope, convulsion, psychomotor hyperactivity, anosmia, hypoaesthesia
Eye disorders			Visual impairment, blurred vision
Ear and labyrinth disorders		Vertigo, ear disorder	Hearing impairment including deafness and/or tinnitus
Cardiac disorders		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		Hot flush	Hypotension
Respiratory, thoracic and mediastinal disorders		Dyspnoea, epistaxis	
Gastrointestinal disorders	Diarrhoea (resulting in dehydration), abdominal pain/cramps, nausea, vomiting	Constipation, flatulence, dyspepsia, gastritis, dysphagia, abdominal distension, dry mouth, eructation, mouth ulceration, salivary hypersecretion	Pancreatitis, tongue discoloration
Hepato-biliary disorders		Hepatic function abnormal, jaundice cholestatic	Hepatic failure (which has rarely resulted in death) (see section 4.4), fulminant hepatitis, hepatic necrosis
Skin and subcutaneous tissue disorders		Rash, pruritus, urticaria, dermatitis, dry skin, hyperhidrosis, photosensitivity reaction, acute generalised exanthematous	Toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome

		pustulosis (AGEP)	
Musculoskeletal and connective tissue disorders		Osteoarthritis, myalgia, back pain, neck pain	Arthralgia
Renal and urinary disorders		Dysuria, renal pain	Acute renal failure, interstitial nephritis
Reproductive system and breast disorders		Metrorrhagia, testicular disorder	
General disorders and administrative site conditions		Oedema, asthenia, malaise, chest pain, fatigue, face oedema, pyrexia, pain, peripheral oedema	
Investigations	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		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 providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

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.

Treatment

In the event of overdose, the administration of medicinal charcoal, general symptomatic and supportive measures are indicated as required.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, macrolides

ATC code: J01FA10

Mechanism of action

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.

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/mL, 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 population groups**

Renal impairment:

The pharmacokinetics of azithromycin in adult patients with mild-to-moderate renal impairment (GFR 10 to 80 ml/min) were not affected following a single 1 g dose of immediate release azithromycin. Statistically significant differences in $AUC_{0\ to\ 120}$ (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

Flavour banana powder, flavour strawberry, flavour vanilla powder, hydroxypropyl cellulose, sucrose, trisodium phosphate dodecahydrate, xanthan gum.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

The reconstituted suspension should be stored at or below 30 ºC and any unused suspension discarded after 7 days.

6.4. Special precautions for storage

Store at or below 30 °C.

For storage of the reconstituted suspension see section 6.3.

6.5. Nature and contents of container

HDPE bottles containing powder to produce 15 ml or 30 ml reconstituted suspension, packed in an outer carton.

6.6. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Reconstituting instructions for AZITHROMYCIN S ASPEN 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 (1 200 mg)	200 mg/5 ml

Shake well before use. Oversized bottles provide shake space. Keep tightly closed.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

48/20.1.1/0224

9. DATE OF FIRST AUTHORISATION

24 July 2020

10. DATE OF REVISION OF TEXT

24 July 2020

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