Summary of Product Characteristics

1. Name of the Medical Product
Zitho 500mg injection

2. Qualitative & Quantitative Composition:
Each vial contains;
Azithromycin
Eq. to Azithromycin anhydrous.....500mg

Excipient of known effect
Sodium

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form:
Injection

Visual Description
White or almost white lyophilized cake

4. Clinical Particulars
4.1 Therapeutic Indications:
Azithromycin as powder for solution for infusion is indicated for the treatment of community-acquired pneumonia due to susceptible microorganisms, (see Section 5.1) in adult patients where initial intravenous therapy is required.
Azithromycin as powder for solution for infusion is indicated for the treatment of pelvic inflammatory disease (PID) due to susceptible microorganisms (see Section 5.1), in patients where initial intravenous therapy is required.
Consideration should be given to official guidance regarding the appropriate use of antibacterial agents.

4.2 Posology and Method of administration:
Posology
The recommended dose of Azithromycin (azithromycin as powder for solution for infusion) for the treatment of adult patients with community-acquired pneumonia due to the indicated susceptible microorganisms is of 500 mg administered as a single intravenous daily dose for at least two consecutive days. The intravenous therapy should be followed by the oral administration of azithromycin in a single daily dose of 500 mg up to 7 to 10 days of treatment. Transition to oral therapy should be carried out when indicated by the doctor and according to the clinical response.
The recommended dose of Azithromycin (azithromycin as powder for solution for infusion) for the treatment of adult patients with pelvic inflammatory disease (PID) due to the indicated susceptible microorganisms is of 500 mg administered as a single intravenous daily dose for one or two days. The intravenous therapy should be followed by the oral administration of azithromycin in a single daily dose of 250 mg up to 7 days of treatment. Transition to oral therapy should be carried out when indicated by the doctor and according to the clinical response.
Use in the elderly

No dose adjustment is required in elderly patients that require therapy with azithromycin.

Use in patients with renal impairment

No dose adjustment is recommended in patients with mild to moderate renal impairment (GFR 10 - 80 ml/min). Caution should be exercised when azithromycin is administered to patients with severe renal impairment (GFR < 10 ml/min) (see Section 4.4 and Section 5.2).

Use in patients with hepatic impairment

Dose adjustment is not required for patients with mild to moderate hepatic dysfunction but the medicinal product should be used with caution in patients with significant hepatic diseases (see Section 4.4).

Use in children

The efficacy and safety of azithromycin as powder for solution for infusion for the treatment of infections in children and adolescents has not been established.

Method of administration

Once Azithromycin (azithromycin as powder for solution for infusion) is reconstituted and diluted is intended to be administered by intravenous infusion. It should not be administered as an intravenous bolus or an intramuscular injection.

The concentration of the solution for infusion and the infusion rate of azithromycin as powder for solution for infusion should be 1 mg/ml for 3 hours or 2 mg/ml for 1 hour.

Preparation of the solution for intravenous administration

Reconstitution

The initial solution of azithromycin is prepared by adding 4.8 ml of sterile water for injections to the 500 mg vial and shaking the vial until all the drug is dissolved. It is recommended that a standard 5 ml (non-automated) syringe be used to ensure that the exact volume of 4.8 ml of sterile water for injections is dispensed. Each ml of reconstituted solution contains azithromycin dihydrate equivalent to 100 mg azithromycin (100 mg/ml).

Parenteral administration drugs should be inspected visually for particulate in suspension prior to administration. If particulate in suspension is evident in reconstituted solution, the drug solution should be discarded.

The reconstituted solution must be further diluted prior to administration as instructed below.

Dilution

To provide azithromycin over a concentration range of 1.0 - 2.0 mg/ml, transfer 5 ml of the 100 mg/ml azithromycin solution to the appropriate amount of any of the diluents listed in Section 6.6 Special precautions for disposal and other handling.

Final infusion solution concentration (mg/ml)	Amount of diluent (ml)
1.0 mg/ml	500 ml
2.0 mg/ml	250 ml

It is recommended that a 500 mg dose of azithromycin as powder for solution for infusion, diluted according to the instructions above, be administered as an intravenous infusion over at least 60 minutes.

4.3 Contraindications:

Azithromycin is contraindicated in patients with a known hypersensitivity to azithromycin, erythromycin or any of the macrolide or ketolide antibiotics, or to any of the excipients (listed in Section 6.1).

Azithromycin should not be co-administered with ergot derivatives because of the theoretical possibility of ergotism.

4.4 Special warnings & precautions for use

Hypersensitivity

As with erythromycin and other macrolides, rare serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal), dermatologic reactions including acute generalised exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

If an allergic reaction occurs the drug should be discontinued and appropriate therapy should be instituted. Physicians should 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 should be undertaken with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin (see Section 4.8). Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.

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. Azithromycin administration should be stopped if liver dysfunction has emerged.

Ergot derivatives

In patients receiving ergotamine 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. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administrated

Prolongation of the QT interval

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarisation (see Section 4.8); therefore, caution is required when treating patients:

• With congenital or documented QT prolongation

• Currently receiving treatment with other active substance known to prolong QT interval such as antiarrhythmics of classes Ia and III, cisapride and terfenadine

• With electrolyte disturbance, particularly in case of hypokalaemia and hypomagnesemia

• With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

Superinfection

As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms including fungi is recommended.

***Clostridium difficile* associated diarrhoea**

Clostridium difficile associated diarrhoea (Pseudomembranous colitis - CDAD) has been reported with the use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhoea to fatal colitis.

Treatment with antibiotics alters the normal flora of the colon allowing an overgrowth of *C. difficile*.
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 two months after the administration of antibacterial agents. Discontinuation of therapy with azithromycin and the administration of specific treatment for *C. difficile* should be considered.

Streptococcal infections

Penicillin is usually the first choice for treatment of pharyngitis/tonsillitis 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 (GFR <10 ml/min) a 33% increase in systemic exposure to azithromycin was observed (see Section 5.2).

Myasthenia gravis

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy (See Section 4.8).
Safety and efficacy of azithromycin intravenous infusion for treatment of infections in children have not been established.
Safety and efficacy for prevention or treatment of MAC in children have not been established.
Azithromycin (azithromycin as powder for solution for infusion) should be reconstituted and diluted according to the instructions and should be administered as an intravenous infusion over at least 60 minutes.
It should not be administered as an intravenous bolus or an intramuscular injection (See Sections 4.2 and 6.6).
This medicinal product contains 114 mg (4.96 mmol) sodium per vial, equivalent to approximately 5.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
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).

4.5 Interactions with other medicinal products and other forms of Interactions

Antacids: In a pharmacokinetic study investigating the effects of simultaneous administration of antacid with oral azithromycin, no effect on overall bioavailability was seen, although peak serum concentrations were reduced by approximately 24%. In patients taking azithromycin by oral administration, azithromycin should be taken at least 1 hour before or 2 hours after the antacid.
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.

Didanosine *(Dideoxyinosine)***:** Co-administration of 1200 mg/day azithromycin with 400 mg/day didanosine in six HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared to placebo.
Digoxin and colchicine: Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin and colchicine, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and P-glycoprotein substrates such as digoxin are administered concomitantly, the possibility of elevated serum digoxin concentrations should be considered. Clinical monitoring, and possibly serum digoxin levels, during treatment with azithromycin and after its discontinuation are necessary.
Zidovudine: Single 1000 mg doses and multiple 1200 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.
Azithromycin does not interact significantly with the hepatic cytochrome P450 system. It is not believed to undergo the pharmacokinetic drug interactions as seen with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inactivation via cytochrome-metabolite complex does not occur with azithromycin.
Ergot derivatives *(Ergotamine)***:** Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended (See Section 4.4).
Pharmacokinetic studies have been conducted between azithromycin and the following drugs 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).
Carbamazepine: In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.
Cimetidine: In a pharmacokinetic study investigating the effects of a single dose of cimetidine, given 2 hours before azithromycin, on the pharmacokinetics of azithromycin, no alteration of azithromycin pharmacokinetics was seen.
Coumarin-Type Oral Anticoagulants: In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single 15 mg dose of warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to co-administration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.
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 Cmax and AUC were found to be significantly elevated (by 24% and 21% respectively), however no significant changes were seen in AUC0-5. Consequently, caution should be exercised before considering concurrent administration of these

drugs. If co-administration of these drugs is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.
Efavirenz: Co-administration of a single dose of 600 mg 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 1200 mg azithromycin did not alter the pharmacokinetics of a single dose of 800 mg fluconazole. Total exposure and half-life of azithromycin were unchanged by the co-administration of fluconazole, however, a clinically insignificant decrease in Cmax (18%) of azithromycin was observed.
Indinavir: Co-administration of a single dose of 1200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.
Methylprednisolone: In a pharmacokinetic interaction study in healthy volunteers, azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.
Midazolam: In healthy volunteers, co-administration of azithromycin 500 mg/day for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single 15 mg dose of midazolam.
Nelfinavir: Co-administration of azithromycin (1200 mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment was required.
Rifabutin: Co-administration of azithromycin and rifabutin did not affect the serum concentrations of either drug. Neutropenia was observed in subjects receiving concomitant treatment of azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established (see Section 4.8).
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 Cmax, of sildenafil or its major circulating metabolite.
Terfenadine: Pharmacokinetic studies have reported no evidence of an interaction between azithromycin and terfenadine. There have been rare cases reported where the possibility of such an interaction could not be entirely excluded; however, there was no specific evidence that such an interaction had occurred.
Theophylline: There is no evidence of a clinically significant pharmacokinetic interaction when azithromycin and theophylline are co-administered to healthy volunteers.
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 DS (160 mg/800 mg) for 7 days with azithromycin 1200 mg on Day 7 had no significant effect on peak concentrations, total exposure or urinary excretion of either trimethoprim or sulfamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies.
Hydroxychloroquine and chloroquine: Observational data have shown that co-administration of azithromycin with hydroxychloroquine in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality. Carefully consider the balance of benefits and risks

before prescribing azithromycin for any patients taking hydroxychloroquine. Similar careful consideration of the balance of benefits and risk should also be undertaken before prescribing azithromycin for any patients taking chloroquine, because of the potential for a similar risk with chloroquine.

4.6 Pregnancy and Lactation

Pregnancy

There are no adequate data from the use of azithromycin in pregnant women. In reproduction toxicity studies in animals, azithromycin was shown to pass the placenta, but no teratogenic effects were observed (see Section 5.3). The safety of azithromycin has not been confirmed with regard to the use of the active substance during pregnancy. Therefore, Azithromycin should only be used during pregnancy if definitely indicated.

There is a large amount of data from observational studies performed in several countries on exposure to azithromycin during pregnancy, compared to no antibiotic use or use of another antibiotic during the same period (>7,300 first trimester exposures). While most studies do not suggest an association with adverse foetal effects such as major congenital malformations or cardiovascular malformations, there is limited epidemiological evidence of an increased risk of miscarriage following azithromycin exposure in early pregnancy.

Therefore, azithromycin should only be used during pregnancy if clinically needed and the benefit of treatment is expected to outweigh any small increased risks which may exist.

Breastfeeding

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

Fertility

Animal data do not suggest an effect of the treatment of azithromycin on male and female fertility. Human data are lacking.

4.7 Effects on ability to drive and use machine*:

There is no evidence to suggest that azithromycin may have an effect on a patient's ability to drive or operate machinery.

4.8 Undesirable Effects*:

The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency. Adverse reactions identified from post-marketing experience are included in italics. The frequency grouping is defined using the following convention: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse reactions possibly or probably related to azithromycin based on clinical trial experience and post-marketing surveillance:

System organ class	Adverse reaction	Frequency
	Candidiasis, oral candidiasis, vaginal infection	Uncommon

Infections and infestations	*Pseudomembranous colitis* (See Section 4.4)	Not known
Blood and lymphatic system disorders	Leukopenia, neutropenia	Uncommon
	Thrombocytopenia, haemolytic anaemia	*Not known*
Immune system disorders	Angioedema, hypersensivity	Uncommon
	Anaphylactic reaction (See Section 4.4)	*Not known*
Metabolism and nutrition disorders	Anorexia	Common
Psychiatric disorders	Nervousness	Uncommon
	Agitation	Rare
	Aggression, anxiety	*Not known*
Nervous system disorders	Dizziness, headache, paraesthesia, dysgeusia	Common
	Hypoaesethesia, somnolence, insomnia	Uncommon
	Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis (See Section 4.4)	*Not known*
Eye disorders	Visual impairment	Common
Ear and labyrinth disorders	Deafness	Common
	Hearing impaired, tinnitus	Uncommon
	Vertigo	Rare
Cardiac disorders	Palpitations	Uncommon
	Torsades de pointes (See Section 4.4), *arrhythmia* (See Section 4.4) including *ventricular tachycardia*	*Not known*
Vascular disorders	*Hypotension*	Not known
Gastrointestinal disorders	Diarrhoea, abdominal pain, nausea, flatulence	Very common
	Vomiting, dyspepsia	Common
	Gastritis, constipation	Uncommon
	Pancreatitis, tongue discolouration	Not known
Hepatobiliary disorders	Hepatitis	Uncommon
	Hepatic function abnormal	Rare
	Hepatic failure (See Section 4.4)**, *hepatitis fulminant, hepatic necrosis, jaundice cholestatic*	*Not known*
Skin and subcutaneous tissue disorders	Pruritus and rash	Common
	Stevens-Johnson syndrome (SJS), photosensitivity reaction, urticaria	Uncommon
	Acute Generalised Exanthematous Pustulosis (AGEP)	Rare
	Drug reaction with eosinophilia and systemic symptoms (DRESS)	Very Rare
	Toxic epidermal necrolysis (TEN), erythema multiforme	*Not known*
Musculoskeletal and connective tissue disorders	Arthralgia	Common
Renal and urinary disorders	*Renal failure acute, nephritis interstitial*	*Not known*
General disorders and administration site conditions	Pain and inflammation on the local injection site*, fatigue	Common
	Chest pain, oedema, malaise, asthenia	Uncommon
Investigations	Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased	Common
	Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal	Uncommon
	Electrocardiogram QT prolonged (See Section 4.4)	*Not known*

* have been reported with the intravenous administration of azithromycin.
** which has rarely resulted in death

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board,

Pharmacovigilance Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

4.9 Overdose:
Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea. In the event of overdose, general symptomatic treatment 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 a macrolide antibiotic belonging to the azalide group. The molecule is constructed by adding a nitrogen atom to 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. The mechanism of action of azithromycin is based upon the suppression of bacterial protein synthesis by means of binding to the ribosomal 50s sub-unit and inhibition of peptide translocation.
Mechanism of resistance
There are two dominant genes that determine the resistance of isolates of *Streptococcus pneumoniae* and *Streptococcus pyogenes*: mef and erm. The mef gene encodes a flow pump that mediates resistance to macrolides 14- and 15- only. The mef gene has also been described in a variety of other species. The erm gene codes for a 23S-rRNA methyltransferase that adds methyl groups to adenine 2058 of 23S rRNA (numbering system of *E. coli* rRNA).
The methylated nucleotide is located in a domain V and is thought to interact with the lincosamides and streptogramin B, in addition to macrolides, resulting in a phenotype known as MLSB resistance. Genes erm (B) and erm (A) are clinical isolates of *S. pneumoniae* and *S. pyogenes*.
The pump AcrAB-TolC of *Haemophilus influenzae* is responsible for the innate MIC values higher for macrolides.
In clinical isolates, mutations in 23S rRNA, specifically in nucleotides 2057 – 2059 or 2611 in domain V, or mutations in ribosomal protein L4 or L22, are rare.
A complete cross resistance exists among erythromycin, azithromycin, other macrolides and lincosamides for *Streptococcus pneumoniae*, beta-haemolytic streptococci of group A, Enterococcus *spp.* and *Staphylococcus aureus*, including methicillin resistant *Staphylococcus aureus* (MRSA). Penicillin susceptible *Streptococcus pneumoniae* are more likely to be susceptible to azithromycin than are penicillin resistant strains of *Streptococcus pneumoniae*. Methicillin resistant *Staphylococcus aureus* (MRSA) is less likely to be susceptible to azithromycin than methicillin susceptible *Staphylococcus aureus* (MSSA).
Breakpoints
The EUCAST susceptibility breakpoints for typical bacterial pathogens are:
- *Staphylococcus* spp.; susceptible ≤ 1 mg/l; resistant > 2 mg/l
- *Haemophilus* spp.: susceptible ≤ 0,12 mg/l; resistant > 4 mg/l
- *Streptococcus pneumoniae* and *Streptococcus A, B, C, G*: susceptible ≤ 0.25 mg/l; resistant > 0.5 mg/l
- *Moraxella catarrhalis:* ≤ 0.5 mg/l; resistant > 0.5 mg/l
- *Neisseria gonorrhoeae:* ≤ 0.25 mg/l; resistant > 0.5mg/l

Susceptibility

The bacterial species susceptibility to azithromycin is presented below. The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Table: Antibacterial spectrum

Commonly susceptible species
Aerobic Gram-positive microorganisms
Staphylococcus aureus (methicillin-susceptible)
Streptococcus pneumoniae (penicillin-susceptible)
Streptococcus pyogenes (Group A)
Aerobic Gram-negative microorganisms
Haemophilus influenzae
Haemophilus parainfluenzae
Legionella pneumophila
Moraxella catarrhalis
Neisseria gonorrhoeae
Pasteurella multocida
Anaerobic microorganisms
Clostridium perfringens
Fusobacterium spp.
Prevotella spp.
Porphyromonas spp.
Other microorganisms
Chlamydia pneumoniae
Chlamydia trachomatis
Chlamydia psittaci
Mycoplasma pneumoniae
Mycoplasma hominis
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Streptococcus pneumoniae penicillin-intermediate and penicillin-resistant
Inherently resistant organisms
Aerobic Gram-positive microorganisms
Enterococcus faecalis
Staphylococci **MRSA, MRSE** *
Anaerobic microorganisms
Bacteroides fragilis group

*** Methicillin-resistant staphylococci have a very high prevalence of acquired resistance to macrolides and have been placed here because they are rarely susceptible to azithromycin.**

5.2 Pharmacokinetics Properties*:

Absorption

Bioavailability after oral administration is approximately 37%. Peak plasma concentrations are attained 2 to 3 hours after taking the medicinal product. The administration of azithromycin capsules after a substantial meal reduces bioavailability.

In patients hospitalized with community-acquired pneumonia treated with a single daily intravenous infusion of 500 mg azithromycin, over one hour, in a solution with a concentration of 2 mg/ml, for 2 to 5 days, the mean Cmax ± D achieved was of 3.63 ± 1.60 µg/ml, while the trough levels concentration at 24 hours was 0.20 ± 0.15 µg/ml and the AUC24 of 9.60 ± 4.80 µg.h/ml.

Mean Cmax, trough levels concentration at 24 hours and AUC24 values were of 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 intravenous infusion of 500 mg azithromycin at a concentration of 1 mg/ml, for 3 hours.

Distribution

Orally administered azithromycin is widely distributed throughout the body. In pharmacokinetic studies it has been demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (as much as 50 times than those measured in plasma), which indicates that the agent strongly binds to tissues. Concentrations in target tissues such as lung, tonsil, and prostate exceed the MIC90 for likely pathogen agents after a single dose of 500 mg. High azithromycin concentrations were detected in gynaecological tissue 96 hours after a single dose of 500 mg azithromycin.

In animal tests, high concentrations of azithromycin have been found in phagocytes. It has also been established that during active phagocytosis higher concentrations of azithromycin are released from inactive phagocytes. In animal models this results in high concentrations of azithromycin being delivered to the site of infection.

Biotransformation/Elimination

The terminal plasma elimination half-life closely reflects the elimination half-life from tissues of 2-4 days.

In a multiple-dose study in 12 normal volunteers using 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 higher than the reported 6% as being excreted unchanged in urine after oral administration of azithromycin. Particularly high concentrations of unchanged azithromycin have been found in human bile. Also in bile, ten metabolites were detected, which were formed through N- and O-demethylation, hydroxylation of desosamine and aglycone rings and cleavage of cladinose conjugate. Comparison of the results of liquid chromatography and microbiological analyses carried has shown that the metabolites do not contribute to azithromycin microbiological activity.

Pharmacokinetics in special patient groups

Renal insufficiency

Following a single oral dose of azithromycin 1 g, mean Cmax and AUC0-120 increased by 5.1% and 4.2% respectively, in subjects with mild to moderate renal impairment (glomerular filtration rate of 10-80 ml/min) compared with normal renal function (GFR>80ml/min). In subjects with severe renal impairment, the mean Cmax and AUC0-120 increased 61% and 35% respectively compared to normal.

Hepatic insufficiency

In patients with mild to moderate hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to normal hepatic function. In these patients, urinary recovery of azithromycin appears to increase perhaps to compensate for reduced hepatic clearance.

Elderly

The pharmacokinetics of azithromycin in elderly men was similar to that of young adults; however, in elderly women, although higher peak concentrations (increased by 30-50%) were observed, no significant accumulation occurred. In elderly volunteers (>65 years), higher (29 %) AUC values were always observed after a 5-day course than in younger volunteers (<45 years). However, these differences are not considered to be clinically relevant; no dose adjustment is therefore recommended.

5.3 Preclinical safety data
Phospholipidosis (intracellular phospholipid accumulation) has been observed in several tissues (e.g. eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and/or pancreas) of mice, rats, and dogs given multiple doses of azithromycin. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs. The effect has been shown to be reversible after cessation of azithromycin treatment. The significance of the finding for animals and for humans is unknown.
Electrophysiological investigations have shown that azithromycin prolongs the QT interval.
Carcinogenic potential
Long-term studies in animals have not been performed to evaluate carcinogenic potential.
Mutagenic potential
There was no evidence of a potential for genetic and chromosome mutations in *in-vivo* and *in-vitro* test models.
Reproductive toxicity
In animal studies of the embryotoxic effects of the substance, no teratogenic effect was observed in mice and rats. In rats, azithromycin dosages of 100 and 200 mg/kg/day led to mild retardation of foetal ossification and maternal weight gain. In peri- and post-natal studies in rats, mild retardation was observed following treatment with 50 mg/kg/day azithromycin and above.

6. Pharmaceutical particulars:
6.1 List of Excipients:
Citric acid
NaOH
Water for Injection

6.2 Incompatibilities:
Azithromycin reconstituted solution can be diluted according to the instructions and compatible solutions for infusion, indicated in Section 6.6 Special precautions for disposal and other handling.
This medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6.
Other intravenous substances, additives or other medications should not be added or infused simultaneously through the same intravenous line.

6.3 Shelf life:
24 months

- Concentrated solution after reconstitution (according to the instructions): azithromycin as powder for solution for infusion is chemically and physically stable during 24 hours, when stored below 25 °C.
- Diluted solutions, prepared according to the instructions, are chemically and physically stable for 24 hours at or below 25°C, or for 72 hours if stored at 2-8°C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless the reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special Precautions for storage:
This medicinal product does not require any special storage conditions prior to reconstitution.
For storage conditions after reconstitution and dilution of the medicinal product, see Section 6.3.

6.5 Nature and contents of container:
White cake filled in 10 ml USP type I clear colourless tubular glass vial sealed with 20 mm fully slotted grey butyl rubber stopper and 20 mm flip off seal

6.6 Special precautions for disposal:
Azithromycin as powder for solution for infusion is supplied in single dose vials.
Preparation of reconstituted solution
The initial reconstituted solution is prepared by adding 4.8 ml of sterile water for injections to the 12 ml vial initial content using a standard 5 ml syringe (non-automated) and shaking the vial until all the drug is dissolved. Each ml reconstituted solution contains azithromycin dihydrate equivalent to 100 mg azithromycin (100 mg/ml).
The reconstituted medicinal product is chemically and physically stable during 24 hours, when stored below 25 °C. Diluted solutions, prepared according to the instructions, are chemically and physically stable for 24 hours at or below 25°C, or for 72 hours if stored at 2-8°C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless the reconstitution/dilution has taken place in controlled and validated aseptic conditions.
The reconstituted solution must be further diluted prior to administration.

Dilution of reconstituted solution
To provide azithromycin at a concentration of 1.0 or 2.0 mg/ml, transfer 5 ml of the 100 mg/ml azithromycin solution to the appropriate amount of any of the diluents listed below.

Final infusion solution concentration (mg/ml)	Amount of diluent (ml)
1.0 mg/ml	500 ml
2.0 mg/ml	250 ml

The reconstituted solution can be diluted with:
0.9 % sodium chloride
0.45 % sodium chloride
5% dextrose in water
Lactated Ringer's solution
5% dextrose in 0.3% sodium chloride
5% dextrose in 0.45% sodium chloride
Parenteral administration drugs should be inspected visually for particulate in suspension prior to administration. If particulate in suspension is evident in the reconstituted solution, it should be discarded.
It is recommended that the 500 mg dose of azithromycin as powder for solution for infusion, diluted as described above, be administered as an intravenous infusion over at least 60 minutes.

Azithromycin should not be administered as an intravenous bolus or an intramuscular injection.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder:
Sai Pharmaceuticals Limited
Unit C1, Whitefield Place, 28 School Lane, Nairobi, Kenya

Manufacturing Site Address:
Indasi Lifescience Pvt.Ltd.
Plot No. 73-76, Silver Industrial Estate, Bhimpore, Daman.(U.T) 396210

8. Marketing Authorization Numbers:
H2022/CTD8203/16405

9. Date of first registration /renewal of the registration:
2022 June 02

10. Date of revision of text:
2022 June 02