Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Mythro
(Azithromycin Tablets 500mg)

2. Qualitative and quantitative composition

Each Film-coated tablet contains Azithromycin (as Azithromycin Dihydrate) 500mg

For a full list of excipients, see section 6.1

3. Pharmaceutical form

Film-coated tablets
Red coloured, elongated, biconvex, film-coated tablets, scored on one side and plain on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Azithromycin is indicated for the treatment of the following infections when known or likely to be due to one or more susceptible microorganisms (see section 5.1):

- bronchitis
- community-acquired pneumonia
- sinusitis
- pharyngitis/tonsillitis (see section 4.4 regarding streptococcal infections)
- otitis media
- skin and soft tissue infections
- uncomplicated genital infections due to *Chlamydia trachomatis* and *Neisseria gonorrhoeae.*

Considerations should be given to official guidance regarding the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology
Azithromycin should be given as a single daily dose.

In common with many other antibiotics Azithromycins should be taken at least one hour before or 2 hours after food.

Children over 45 kg body weight and adults, including elderly patients: The total dose of azithromycin is 1500 mg which should be given over three days (500 mg once daily).

In uncomplicated genital infections due to *Chlamydia trachomatis,* the dose is 1000 mg as a single oral dose. For susceptible *Neisseria gonorrhoeae* the recommended dose is 2000 mg azithromycin as a single oral dose together with 500 mg ceftriaxone intramuscularly as a single dose according to local clinical treatment guidelines. For patients who are allergic to penicillin and/or

cephalosporins, prescribers should consult local treatment guidelines.

Paediatric population
In children under 45 kg body weight:
Azithromycins are not suitable for children under 45 kg.

The Elderly
The same dosage as in adult patients is used in the elderly.
Since elderly patients can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes (see section 4.4).
Renal impairment
No dose adjustment is necessary in patients with a glomerular filtration rate (GFR) of 10-80 ml/min. Caution should be exercised when azithromycin is administered to patients with a GFR of <10 ml/min (see section 4.4 and section 5.2).

Hepatic impairment
Since azithromycin is metabolised in the liver and excreted in the bile, the drug should not be given to patients suffering from severe liver disease. No studies have been conducted regarding treatment of such patients with azithromycin (see section 4.4).

Method of administration
Azithromycins are for oral administration only.

4.3 Contraindications
Hypersensitivity to azithromycin, erythromycin or any of the macrolide or ketolide antibiotics, or to any of the excipients listed in section 6.1.

4.4 Special warnings and 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 Generalized 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.

Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Discontinue azithromycin immediately if signs and 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.
Azithromycin administration should be stopped if liver dysfunction has emerged.

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

Ergot derivatives
In patients receiving ergot derivatives, ergotism has been precipitated by co-administration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergot and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered.

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 (CDAD) has been reported with the use of nearly all antibacterial agents, including azithromycin, and may range in severity form mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C difficile*.

C. difficile produces toxins A and B which 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. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Renal impairment
In patients with a GFR of <10 ml/min, a 33% increase in systemic exposure to azithromycin was observed (see section 5.2).

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, including azithromycin (see section 4.8). The following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which can lead to cardiac arrest (possibly fatal). Azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as patients:

- With congenital or documented QT prolongation
- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of Class IA (quinidine and procainamide) and class III (dofetilide, amiodarone and sotalol), cisapride and terfenadine, antipsychotic agents such as pimozide; antidepressants such as citalopram; and fluoroquinolones such as moxifloxacin and levofloxacin.
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency
- Elderly patients: elderly patients may be more susceptible to drug-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 (see section 4.8).

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.

Paediatric population
Safety and efficacy for the prevention or treatment of Mycobacterium Avium Complex (MAC) in children have not been established.

Azithromycins are for oral administration only.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids: When studying the effect of simultaneously administered antacid on the pharmacokinetics of azithroycin, no overall change has been observed in the bioavailability, although the peak concentrations of azithromycin measured in the plasma fell by 24%. In patients receiving Azithromycin and antacids, Azithromycin should be taken at least 1 hour before or 2 hours after the antacid. Co-administration of azithromycin prolonged-release granules for oral suspension with a single dose of 20 ml
co-magaldrox (aluminium hydroxide and magnesium hydroxide) did not affect the rate and extent of azithromycin absorption.

Cetirizine: In healthy volunteers, co-administration of a 5-day regimen of azithromycin with 20 mg cetirizine at steady-state resulted in no

pharmacokinetic interaction and no significant changes in the QT interval.

Didanosine: Co-administration of daily doses of 1200 mg azithromycin with 400 mg didanosine in six HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared to placebo.

Digoxin and colchicine: (P-glycoprotein substrates): 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 concentrations of the substrate 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: Because of the theoretical possibility of ergotism, the concurrent use of Azithromycin (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). However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin with statins have been reported.

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 administered 2 hours before Azithromycin had no effect on the pharmacokinetics of azithromycin.

Coumarin-type oral anticoagulants: In a pharmacokinetic interaction study, Azithromycin did not alter the anticoagulant effect of a single dose of 15 mg

warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to co-adinistration 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 who 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 AUC0-5 were found to be significantly elevated (by 24% and 21% respectively), however no significant changes were seen in AUC0-∞. Consequently, caution should be exercised before considering co-administration of these two drugs. If
co-administration 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 500 mg/day azithromycin for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single dose of 15 mg 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 500 mg azithromycin 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 1200 mg azithromycin 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

4.6 Pregnancy and Lactation

Pregnancy

In reproduction toxicity studies in animals azithromycin was shown to pass the placenta, but no teratogenic effects were observed.

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. While most studies do not suggest an association with adverse fetal 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.

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.

Breast-feeding

Limited information available from published literature indicates that azithromycin is present in human milk at an estimated highest median daily dose of 0.1 to 0.7 mg/kg/day. No serious adverse effects of azithromycin on the breast-fed infants were observed. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
In fertility studies conducted in rats, reduced pregnancy rates were noted following administration of azithromycin. The relevance of this finding to humans is unknown.

4.7 Effects on ability to drive and use machines

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

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

Azithromycin is well tolerated with a low incidence of side-effects.

The section below lists the adverse reactions identified through clinical trial experience and postmarketing 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); and 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

	Very Common (≥1/10)	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1000 to < 1/100)**	**Rare (≥ 1/10,000 to <1/1,000)**	**Very Rare (<1/10,000)**	**Frequency Not Known**
Infections and Infestations			Candidiasis Vaginal infection Pneumonia Fungal infection Bacterial infection Pharyngitis Gastroenteritis Respiratory disorder Rhinitis Oral candidiasis			Pseudomembrano -us colitis (see section 4.4)

Blood and 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 Insomnia,	Agitation		Aggression Anxiety Delirium Hallucination
Nervous System Disorders		Headache	Dizziness Somnolence Dysgeusia Paraesthesia			Syncope, convulsion Hypoestheia Psychomotor
						hyperactivity Anosmia Ageusia Parosmia Myasthenia gravis (see section 4.4)
Eye Disorders			Visual impairment			
Ear and Labyrinth Disorders			Ear disorder Vertigo			Hearing impairment including deafness and/or tinnitus
Cardiac Disorders			Palpitations			Torsades de pointes (see section 4.4) Arrhythmia (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	Vomiting Abdominal pain Nausea	Constipation Flatulence Dyspepsia Gastritis Dysphagia Abdominal distension Dry mouth Eructation Mouth ulceration Salivary hypersecretion			Pancreatitis Tongue discolouration
Hepatobiliary Disorders				Hepatic function abnormal Jaundice cholestatic		Hepatic failure (which has rarely resulted in death) (see section 4.4) Hepatitis fulminant Hepatic necrosis
Skin and Subcutaneous Tissue Disorders			Rash Pruritus Urticaria, Dermatitis Dry skin Hyperhidrosis	Acute Generalized Exanthematous Pustulosis (AGEP)*§, Drug reaction with eosinophilia and systemic symptoms (see section 4.4), Photosensitivity		SJS, TEN Erythema multiforme
				reaction		
Musculoskeletal and Connective Tissue Disorders			Osteoarthritis, Myalgia Back pain Neck pain			Arthralgia
Renal and Urinary Disorders			Dysuria Renal pain			Renal failure acute Nephritis interstitial

Reproductive system and breast disorders			Metrorrhagia, Testicular disorder			
General Disorders and Administration Site Conditions			Oedema Asthenia Malaise Fatigue Face edema Chest pain 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			

*ADR identified post-marketing

§ADR frequency represented by the estimated upper limit of the 95% confidence interval calculated using the "Rule of 3".

Adverse reactions possibly or probably related to Mycobacterium Avium Complex prophylaxis and treatment based on clinical trial experience and post-marketing surveillance. These adverse reactions differ from those reported with immediate release or the prolonged release formulations, either in kind or in frequency:

	Very Common (≥1/10)	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1000 to < 1/100)**
Metabolism and Nutrition Disorders		Anorexia	
Nervous System Disorders		Dizziness Headache Paraesthesia Dysgeusia	Hypoesthesia
Eye Disorders		Visual impairment	
Ear and Labyrinth Disorders		Deafness	Hearing impaired Tinnitus
Cardiac Disorders			Palpitations
Gastrointestinal Disorders	Diarrhoea Abdominal painNausea Flatulence Abdominal discomfortLoose stools		
Hepatobiliary Disorders			Hepatitis
Skin and Subcutaneous Tissue Disorders		Rash Pruritus	SJS Photosensitivity reaction
Musculoskeletal and Connective Tissue Disorders		Arthralgia	
General Disorders and Administration Site Conditions		Fatigue	Asthenia Malaise

4.9 Overdose

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. In the event of overdosage, general symptomatic and supportive measures are indicated as required.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use. ATC code: J01FA10

Mode 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.

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 randomized, placebo-controlled parallel trial in 116 healthy subjects who received either chloroquine (1000 mg) alone or in combination with azithromycin (500 mg, 1000 mg, and 1500 mg once daily).
Co-administration of azithromycin 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, 1000 mg and 1500 mg azithromycin, respectively.

Mechanism of resistance:
The two most frequently encountered mechanisms of resistance to macrolides, including azithromycin, are target modification (most often by methylation of 23S rRNA) and active efflux. The occurrence of these resistance mechanisms varies from species to species and, within a species, the frequency of resistance varies by geographical location.

The most important ribosomal modification that determines reduced binding of macrolides is post-transcriptional (N_6)
-dimethylation of adenine at nucleotide A2058 (*Escherichia. coli* numbering system) of the 23S rRNA by methylases encoded by *erm* (*e*rythromycin *r*ibosome *m*ethylase) genes. Ribosomal modifications often determine cross resistance (MLS_B phenotype) to other classes of antibiotics whose ribosomal binding sites overlap those of the macrolides: the lincosamides (including clindamycin), and the streptogramin B (which include, for example, the quinupristin component of quinupristin/dalfopristin).
Different *erm* genes are present in different bacterial species, in particular streptococci and staphylococci. Susceptibility to macrolides can also be affected by less frequently encountered mutational changes in nucleotides A2058 and A2059, and at some other positions of 23S rRNA, or in the large subunit ribosomal proteins L4 and L22.

Efflux pumps occur in a number of species, including Gram-negatives, such as *Haemophilus influenzae* (where they may determine intrinsically higher minimal inhibitory concentrations [MICs]) and staphylococci. In streptococci and enterococci, an efflux pump that recognizes 14- and 15-membered macrolides (which include, respectively, erythromycin and azithromycin) is encoded by *mef* (A) genes.

Methodology for determining the in vitro susceptibility of bacteria to azithromycin
Susceptibility testing should be conducted using standardized laboratory

methods, such as those described by the Clinical and Laboratory Standards Institute (CLSI). These include dilution methods (MIC determination) and disk susceptibility methods.
Both CLSI and theEuropean Committee on Antimicrobial Susceptibility Testing (EUCAST) provide interpretive criteria for these methods.

Based on a number of studies, it is recommended that the in vitro activity of azithromycin be tested in ambient air, to ensure physiological pH of the growth medium. Elevated CO_2 tensions, as often used for streptococci and anaerobes, and occasionally for other species, result in a reduction in the pH of the medium. This has a greater adverse effect on the apparent potency of azithromycin than on that of other macrolides.

The CLSI susceptibility breakpoints, based on broth microdilution or agar dilution testing, with incubation in ambient air, are given in the table below.

CLSI Dilution Susceptibility Interpretive Criteria			
	Broth microdilution MIC (mg/L)		
Organism	**Susceptible**	**Intermediate**	**Resistant**
CLSI dilution susceptibility interpretive criteria			
	Broth microdilution MIC (mg/L)		
Organism	**Susceptible**	**Intermediate**	**Resistant**
Haemophilus species	≤ 4	-	_b
Moraxella catarrhalis	≤ 0.25	-	-
Neisseria meningitidis	≤ 2	-	_b
Staphylococcus aureus	≤ 2	4	≥ 8
Streptococci [a]	≤ 0.5	1	≥ 2
[a] Includes *Streptococcus pneumoniae*, b-hemolytic streptococci and viridans streptococci. [b] The current absence of data on resistant strains precludes defining any category other than susceptible. If strains yield MIC results other than susceptible, they should be submitted to a reference laboratory for further testing. Incubation in ambient air. CLSI = Clinical and Laboratory Standards Institute; MIC = Minimal inhibitory concentration. Source: CLSI, 2012; CLSI, 2010			

Susceptibility can also be determined by the disk diffusion method, measuring inhibition zone diameters after incubation in ambient air. Susceptibility disks contain 15 micrograms of azithromycin. Interpretive criteria for inhibition zones, established bythe CLSI on the basis of their correlation with MIC susceptibility categories, are listed in the table below.

CLSI Disk Zone Interpretive Criteria			
	Disk inhibition zone diameter (mm)		
Organism	**Susceptible**	**Intermediate**	**Resistant**
Haemophilus species	≥ 12	-	-
Moraxella catarralis	≥ 26	-	-
Neisseria meningitidis	≥ 20	-	-
Staphylococcus aureus	≥ 18	14 - 17	£ 13
Streptococci	≥ 18	14 - 17	£ 13

[a] Includes *Streptococcus pneumoniae*, b-hemolytic streptococci and viridans streptococci.
Incubation in ambient air.
CLSI = Clinical and Laboratory Standards Institute; mm = Millimeters.
Source: CLSI, 2012; CLSI, 2010

The validity of both the dilution and disk diffusion test methods should be verified using quality control (QC) strains, as indicated by the CLSI. Acceptable limits when testing azithromycin against these organisms are listed in the table below.

Quality Control Ranges for Azithromycin Susceptibility Tests (CLSI)	
Broth microdilution MIC	
Organism	**Quality control range (mg/L azithromycin)**
Haemophilus influenzae ATCC 49247	1 - 4
Staphylococcus aureus ATCC 29213	0.5 - 2
Streptococcus pneumoniae ATCC 49619	0.06 - 0.25
Disk inhibition zone diameter (15 microgram disk)	
Organism	**Quality control range (mm)**
Haemophilus influenzae ATCC 49247	13 - 21
Staphylococcus aureus ATCC 25923	21 - 26
Streptococcus pneumoniae ATCC 49619	19 – 25
Quality control ranges for azithromycin susceptibility tests (CLSI)	
Broth microdilution MIC	
Organism	**Quality control range (mg/L azithromycin)**

Incubation in ambient air.
CLSI = Clinical and Laboratory Standards Institute; MIC = Minimal inhibitory concentration; mm = Millimeters. Source: CLSI, 2012.

The EUCAST has also established susceptibility breakpoints for azithromycin based on MIC determination. The EUCAST susceptibility criteria are listed in the table below.

EUCAST Susceptibility Breakpoints for Azithromycin		
	MIC (mg/L)	

	Susceptible	**Resistant**
Staphylococcus species	≤ 1	> 2
Streptococcus pneumoniae	≤ 0.25	> 0.5
b-hemolytic streptococci [a]	≤ 0.25	> 0.5
Haemophilus influenzae	≤ 0.12	> 4
Moraxella catarrhalis	≤ 0.25	> 0.5
Neisseria gonorrhoeae	≤ 0.25	> 0.5
Includes Groups A, B, C, G. EUCAST = European Committee on Antimicrobial Susceptibility Testing;MIC = Minimal inhibitory concentration. Source: EUCAST Website. **EUCAST Clinical Breakpoint Table v. 2.0, valid from 2012-01-01** www.eucast.org/…/EUCAST…/Breakpoint_table_v_2.0_120221.pdf		

Antibacterial Spectrum

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.

Azithromycin demonstrates cross resistance with erythromycin-resistant Gram-positive isolates. As discussed above, some ribosomal modifications determine cross resistance with other classes of antibiotics whose ribosomal binding sites overlap those 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 *Streptococcus agalactiae.*

Organisms that are commonly susceptible to azithromycin include:

Aerobic and facultative Gram-positive bacteria (erythromycin-susceptible isolates): *S aureus*, *Streptococcus agalactiae*,* *S pneumoniae**, *Streptococcus pyogenes**, other b-hemolytic streptococci (Groups C, F, G), and viridans streptococci.
Macrolide-resistant isolates are encountered relatively frequently among aerobic and facultative Gram-positive bacteria, in particular among methicillin-resistant *S. aureus* (MRSA) and penicillin-resistant *S. pneumoniae* (PRSP).

Aerobic and facultative Gram-negative bacteria: *Bordetella pertussis*, *Campylobacter jejuni*, *Haemophilus ducreyi**, *Haemophilus influenzae**, *Haemophilus parainfluenzae**, *Legionella pneumophila*, *Moraxella catarrhalis**, and *Neisseria gonorrhoeae**.

Pseudomonas spp. and most *Enterobacteriaceae* are inherently resistant to azithromycin, although azithromycin has been used to treat *Salmonella enterica* infections.

Anaerobes: *Clostridium perfringens*, *Peptostreptococcus* spp. and *Prevotella bivia*.

Other bacterial species: *Borrelia burgdorferi*, *Chlamydia trachomatis*, *Chlamydophila pneumoniae**, *Mycoplasma pneumoniae**, *Treponema pallidum*, and *Ureaplasma urealyticum*.

Opportunistic pathogens associated with HIV infection: MAC* and the eukaryotic microorganisms *Pneumocystis jirovecii* and *Toxoplasma gondii*.

*The efficacy of azithromycin against the indicated species has been demonstrated in clinical trials.

Paediatric population
Following the assessment of studies conducted in children, the use of azithromycin is not recommended for the treatment of malaria, neither as monotherapy nor combined with chloroquine or artemisinin-based drugs, as non-inferiority to anti-malarial drugs recommended in the treatment of uncomplicated malaria was not established.

5.2 Pharmacokinetic properties

Absorption
Bioavailability after oral administration is approximately 37%. Peak plasma concentrations are attained 2 to 3 hours after taking the medicinal product.

Distribution
Orally administered azithromycin is widely distributed throughout the body. In pharmacokinetic studies it has been demonstrated that the concentrations of azithromycin measured in tissue are noticeably higher (as much as 50 times) than those measured in plasma, which indicates that the agent strongly binds to tissues.

Binding to serum proteins varies according to plasma concentration and ranges from 12% at 0.5 microgram/ml up to 52% at 0.05 microgram azithromycin/ml serum. The mean volume of distribution at steady state (VVss) has been calculated to be 31.1 l/kg.

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

Approximately 12% of an intravenously administered dose of azithromycin is excreted unchanged in urine within the following three

days. 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 has shown that the metabolites of azithromycin are not microbiologically active.

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.

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 humans is unknown.

Carcinogenic potential
Long-term studies in animals have not been performed to evaluate carcinogenic potential as the drug is indicated for short-term treatment only and there were no signs indicative of carcinogenic activity.

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 for embryotoxic effects of the substance, no teratogenic effect was observed in mice and rats. In rats, azithromycin doses of 100 and 200 mg/kg bodyweight/day led to mild retardation of foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardation following treatment with 50 mg/kg/day azithromycin and above was observed.

6. Pharmaceutical Particulars

6.1 List of Excipients

Microcrystalline cellulose BP
Povidone (PVP K-30)
Isopropyl Alcohol
Croscarmellose Sodium

Sodium Starch Glycolate
Purified Talc
Hydrophobic Colloidal Anhydrous Silica
Magnesium Stearate
Colour Opadry Red (85G55335)

6.2 Incompatibilities
Not Applicable

6.3 Shelf-Life
36 months

6.4 Special Precautions for storage
Store in a dry place below 30°C. Protect from light.

6.5 Nature and Content of container
Each Alu-PVC blister contains 3 tablets, packed in a carton with a package insert.

6.6 Special precautions for disposal and other handling
No Special requirements

7. Marketing Authorization Holder

Manufacturing Authorization Holder
Name: Simba Pharmaceuticals Ltd
Address: Almont Park 1st floor, Church Road, Off Waiyaki Way, Westlands
Nairobi, Kenya.
Telephone: +254783327327/+254716639225

Manufacturing Site Address:
Name: Next Wave
Address: Rampur Ghat Road, Paonta Sahib Dist. Sirmour, H.P-173025 India

8. Marketing Authorization Number
CTD9436

9. Date of first authorization/renewal of the authorization
02/08/2023

10. Date of revision of the text
13/09/2023

11. Dosimetry
Not Applicable

12. Instructions for preparation of Radiopharmaceuticals

Not Applicable