Summary of Product Characteristics

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

ZILACID (Azithromycin Tablets USP 500 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:
Azithromycin USP (As Dihydrate)
Eq. to Anhydrous Azithromycin 500mg

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film Coated Tablets

Pink coloured, elongated, biconvex, film coated tablets score line on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Azithromycin Film-coated tablets are indicated for the following bacterial infections induced by micro-organisms susceptible to azithromycin (see sections 4.4 and 5.1):
- infections of the lower respiratory tract: acute bronchitis and mild to moderate community acquired pneumonia;
- infections of the upper respiratory tract: sinusitis and pharyngitis/tonsillitis;
- acute otitis media;
- infections of the skin and soft tissues of mild to moderate severity e.g. folliculitis, cellulites, erysipelas;
- uncomplicated Chlamydia trachomatis urethritis and cervicitis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents. Azithromycin is not the first choice for the empiric treatment of infections in areas where the prevalence of resistant isolates is 10% or more (see section 5.1).

4.2 Posology and Method of administration

Azithromycin Film-coated tablets should be taken in a single daily dose. The tablets should be swallowed whole and may be taken with or without food. The length of treatment for various infectious diseases is set out below.

Children and adolescents with a body weight above 45 kg, adults and the elderly:
The total dosage of azithromycin is 1500 mg, staggered over three days (500 mg once daily). Alternatively, the dosage may be staggered over five days (500 mg as a single dose on the first day, and then 250 mg once daily).
In the case of uncomplicated Chlamydia trachomatis urethritis and cervicitis, the dosage is 1000 mg as a single oral dose.

Children and adolescents with a body weight below 45 kg:
Tablets are not indicated for these patients. Other pharmaceutical forms of azithromycin may be used, such as suspensions.

Elderly patients:
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 Special warnings and precautions for use).

Patients with renal impairment:
Dose adjustment is not required in patients with mild to moderate renal impairment (GFR 10-80 ml/min) (see section 4.4).

Patients with hepatic impairment:
Dose adjustment is not required for patients with mild to moderate hepatic dysfunction (see section 4.4).

4.3 Contraindications
The use of azithromycin is contraindicated in patients with hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any excipient listed in Section 6.1

4.4 Special warnings and precautions for use

Allergic reactions:
As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.
Renal failure:
No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10-80 ml/min).
In patients with severe renal impairment (GFR < 10 ml/min) a 33% increase in systemic exposure to azithromycin was observed (see Section 5.2 Pharmacokinetic properties).
Hepatic failure:
Since 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 alkaloids and Azithromycin Film-coated tablets:
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 ergot

and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be coadministered (see section 4.5).

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhea 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 diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

QT prolongation:

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 Undesirable effects). Therefore as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which can lead to cardiac arrest, 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 aspimozide; 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

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 for the prevention or treatment of Mycobacterium Avium Complex in children have not been established.

Pharyngitis/tonsillitis:

Azithromycin is not the substance of first choice for the treatment of pharyngitis and tonsillitis caused by Streptococcus pyogenes. For this and for the prophylaxis of acute rheumatic fever penicillin is the treatment of first choice.

Acute otitis media:

Often, azithromycin is not the substance of first choice for the treatment of acute otitis media.

Sinusitis:

Often, azithromycin is not the substance of first choice for the treatment of sinusitis.

Azithromycin is not indicated for the treatment of infected burn wounds.

In case of sexually transmitted diseases a concomitant infection by T. pallidium should be excluded.

Pneumococcal infections:

As for other macrolides, high resistance rates of Streptococcus pneumoniae (> 30 %) have been reported for azithromycin in some European countries (see section 5.1). This should be taken into

account when treating infections caused by Streptococcus pneumoniae.
Due to cross-resistance existing among macrolides, in areas with a high incidence of erythromycin resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to azithromycin and other antibiotics (see section 5.1).
Superinfections:
Attention should be paid to possible symptoms of superinfections caused by non-sensitive causal agents such as fungi. A superinfection may require an interruption of the azithromycin treatment and initiation of adequate measures.
Neurological or psychiatric diseases:
Azithromycin should be administered with caution to patients suffering from neurological or psychiatric diseases.
Pseudomembranous colitis:
After the use of macrolide antibiotics pseudomembranous colitis has been reported. This diagnosis should therefore be considered for patients who suffer from diarrhoea after start of the treatment with azithromycin. Should pseudomembranous colitis be induced by azithromycin, then anti-peristaltics should be contraindicated.
Long term use:
There is no experience regarding the safety and efficacy of long term use of azithromycin for the mentioned indications. In case of rapid recurrent infections, treatment with another antibiotic should be considered.
Azithromycin Film-coated tablets are not suitable for treatment of severe infections where a high concentration of the antibiotic in the blood is rapidly needed.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucosegalactose malabsorption should not take this medicine.
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.

4.5 Interaction with other medicinal products and other forms of interact.
Antacids:
When studying the effect of simultaneously administered antacid on the pharmacokinetics of azithromycin, no overall change has been observed in the bioavailability, although the peak concentrations of azithromycin measured in the plasma did fall approximately 25 %.
In patients receiving both azithromycin and antacids, the drugs should not be given simultaneaously. Azithromycin should be taken at least 1 hour before or 2 hours after the antacid.
Cetirizine:
In healthy volunteers, coadministration 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.

Ergotamine:

Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended (see Section 4.4 Special warnings and special precautions for use).

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 coadministration 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.

Digoxin (P-gp substrates) 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-gp 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.

Didanosine:

Coadministration of 1200 mg/day azithromycin with 400 mg/day didanosine in 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo

Rifabutin:

Coadministration of azithromycin and rifabutin did not affect the serum concentrations of either active substance. 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 Undesirable effects).

Sildenafil: In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500mg daily for 3 days) on the AUC and Cmax, of sildenafil or its major circulating metabolite.

Theophylline:

There is no evidence of a clinically significant pharmacokinetic interaction when azithromycin and theophylline are co-adminitered to healthy volunteers. Theophylline levels may be increased in patients taking azithromycin.

Even though azithromycin does not appear to inhibit the enzyme CYP3A4, caution is advised when combining the medicinal product with quinidine, cyclosporine, cisapride, astemizole, terfenadine, ergot alkaloids, pimozide or other medicinal products with a narrow therapeutic index predominantly metabolised by CYP3A4.

Cyclosporin:

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 cyclosporin, the resulting cyclosporin Cmax and AUC0-5 were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Efavirenz: Coadministration 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: Coadministration 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 coadministration of fluconazole, however, a clinically insignificant decrease in Cmax (18%) of azithromycin was observed.

Methylprednisolone: In a pharmacokinetic interaction study in healthy volunteers, azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.

Terfenadine:

In pharmacokinetic studies there are no reports of interactions 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. Azithromycin
should be administered with caution in combination with terfenadine.

Cisapride:

Cisapride is metabolized in the liver by the enzyme CYP 3A4. Because macrolides inhibit this enzyme, concomitant administration of cisapride may cause the increase of QT interval prolongation, ventricular arrhythmias and torsade de pointes.

Astemizol, Alfentanil:

No data are available on interactions with astemizol, and alfentanil. Caution should be exercised with concomitant use of these agents and azithromycin in view of the described potentation of its effect during concomitant use of the macrolide antibiotic erythromycin.

Midazolam: In healthy volunteers, coadministration 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.

Triazolam: In 14 healthy volunteers, coadministration 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.

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.

Nelfinavir:

Coadministration of azithromycin (1200 mg) and nelfinavir at steady state (750 mg 3 times daily)

resulted in on average 16% decrease of nelfinavir AUC, an increase of azithromycin AUC and Cmax with 113% and 136%, respectively. No clinical significant adverse effects were observed and no dose adjustment is necessary but patients should be monitored for known side effects of azithromycin.
Trimethoprim/sulfamethoxazole: Coadministration 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.

4.6 Pregnancy and Lactation

Pregnancy:

There are no adequate data and well controlled studies in pregnant women. Animal reproduction toxicity studies show passage across the placenta. No teratogenic effects were observed in rat reproduction studies (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 the benefit outweighs the risk

Lactation:

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

Fertility:

In fertility studies conducted in rat, 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

No studies on the effects on the ability to drive and use machines have been performed. There is no evidence to suggest that azithromycin may have an effect on a patient's ability to drive or operate machinery.
However, the possibility of undesirable effects like dizziness and convulsions should be taken into account when performing these activities.

4.8 Undesirable effects

About 13% of patients included in clinical trials reported adverse events most commonly gastrointestinal disorders.
The table below lists the adverse reactions identified through clinical trial experience and postmarketing surveillance by system organ class and frequency. 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:

Infections and infestations:
Uncommon: Vaginitis, Candidiasis, Vaginal infection, Pneumonia, Fungal infection, Bacterial Infection, Pharyngitis, Gastroenteritis, Respiratory disorder, Rhinitis, Oral candidiasis
Not known: Pseudomembranous colitis (see section 4.4)

Blood and lymphatic system disorders:
Uncommon: Leukopenia, Neutropenia, Eosinophilia
Not known: Thrombocytopenia, Haemolytic anaemia

Immune system disorders:
Uncommon: Angioedema, Hypersensitivity
Not known: Anaphylactic reaction (see section 4.4)

Metabolism and nutrition disorders:
Uncommon: anorexia

Psychiatric disorders:
Uncommon: Nervousness, Insomnia
Rare: Agitation, Depersonalization.
Not known: Aggression, Anxiety, In elderly patients delirium may occur, Hallucination

Nervous system disorders:
Common: Headache
Uncommon: Dizziness/vertigo, somnolence, Dysgeusia, paraesthesia, disruption to the patients taste and smell
Not known: syncope, convulsions, hyperactivity, Hypoestheia, Anosmia Ageusia, Parosmia, Myasthenia gravis (see Section 4.4)

Eye Disorders:
Uncommon: Visual impairment

Ear and labyrinth disorders:
Uncommon: Ear disorder, vertigo
Not known: Hearing impairment, including deafness and/or tinnitus

Cardiac disorders:
Uncommon: palpitations,
Not known: Torsade de pointes, particularly in patients who are susceptible to these conditions, arrhythmia including ventricular tachycardia, electrocardiogram QT prolonged (see section 4.4).

Vascular disorders:
Uncommon: Hot flush

Not known: Hypotension

Respiratory, thoracic and mediastinal disorders:
Uncommon: Dyspnoea, Epistaxis

Gastrointestinal disorders:
Very common: diarrhoea
Common: vomiting, abdominal discomfort
Uncommon: loose stools, constipation, flatulence, Dyspepsia, gastritis dysphagia, Abdominal distension, dry mouth, eructation, Mouth ulceration, salivary hypersecretion, digestive disorders
Rare: discoloration of the teeth
Not known: pancreatitis, tongue discoloration

Hepatobiliary disorders:
Rare: abnormal liver function test values, hepatitis, cholestatic jaundice
Not known: Hepatic failure (which has rarely resulted in death) (see section 4.4) Hepatitis fulminant Hepatic necrosis
Skin and subcutaneous tissue disorders:
Uncommon: allergic reactions including pruritus and rash, Urticaria, Dermatitis Dry skin, Hyperhidrosis
Rare photosensitivity, acute generalised exanthematous pustulosis (AGEP)
Not known: Stevens-Johnson syndrome and toxic epidermal necrolysis, serious skin reactions including erythema multiforme

Musculoskeletal and connective tissue disorders:
Uncommon: Osteoarthritis, Myalgia, Back pain, Neck pain
Not known: arthralgia

Renal and urinary tract disorders:
Uncommon: Dysuria, Renal pain
Not known: intestinal nephritis, acute renal failure

Reproductive system and breast disorders:
Uncommon: Metrorrhagia, Testicular disorder

General disorders and administration site conditions:
Uncommon: fatigue, malaise, oedema, asthenia, face edema, chest pain, pyrexia, pain, peripheral edema

Investigations
Common: Lymphocyte count decreased, Eosinophil count increased Blood bicarbonate decreased, Basophils increased, Monocytes increased, Neutrophils Increased
Uncommon: 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
Uncommon: Post procedural complication

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:
Metabolism and Nutrition Disorders
Common Anorexia

Nervous System Disorders
Common Dizziness, Headache, Paraesthesia, Dysgeusia
Uncommon Hypoesthesia

Eye Disorders
Common Visual impairment

Ear and Labyrinth Disorders
Common Deafness
Uncommon Hearing impaired, Tinnitus

Cardiac Disorders
Uncommon Palpitations
Gastrointestinal Disorders
Very common Diarrhea, Abdominal pain, Nausea, Flatulence, Abdominal discomfort, Loose stools

Hepatobiliary Disorders
Uncommon Hepatitis

Skin and Subcutaneous Tissue Disorders
Common Rash, Pruritus
Uncommon Stevens-Johnson syndrome, Photosensitivity reaction

Musculoskeletal and Connective Tissue Disorders
Common Arthralgia

General Disorders and Administration Site Conditions
Common Fatigue
Uncommon Asthenia, Malaise

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

4.9 Overdose

The undesirable effects at dosages in excess of the recommended dosages were similar to those after normal dosages. The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea. In cases of overdose the administration of medicinal charcoal and general symptomatic treatment and measures to support vital functions are indicated where necessary.

5.0 Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antibacterials for systemic use, macrolides
ATC code: J01FA10

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.

Mode of action:

The mechanism of action of azithromycin is based upon the suppression of bacterial protein synthesis, by binding to the ribosomal 50S sub-unit and thus inhibiting the translocation of peptides.

PK/PD relationship:

For azithromycin the AUC/MIC is the major PK/PD parameter correlating best with the efficacy of azithromycin.

Mechanism of resistance:

Generally, the resistance of different bacterial species to macrolides has been reported to occur by three mechanisms associated with target site alteration, antibiotic modification, or altered antibiotic transport (efflux). The efflux in streptococci is conferred by the mef genes and results in a macroliderestricted resistance (M phenotype). Target modification is controlled by erm encoded methylases.

A complete cross resistance exists among erythromycin, azithromycin, other macrolides and lincosamides for Streptococcus pneumoniae, beta-haemolytic streptococcus 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 azithromcyin than methicillin susceptible Staphylococcus aureus (MSSA).

The induction of significant resistance in both in vitro and in vivo models is <1 dilution rise in MICs for Streptococcus pyogenes, Haemophilus influenzae, and Enterobacterciae after nine sub lethal passages of active substance and three dilution increase for Staphylococcus aureus and development of in vitro resistance due to mutation is rare.

Breakpoints
Azithromycin susceptibility breakpoints for typical bacterial pathogens:
EUCAST:
- 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 > 0.5 mg/l

There are no currently recommended EUCAST breakpoints for the atypical pathogens against which azithromycin has demonstrated clinically significant activity, such as Chlamydia spp., Mycobacterium avium complex, Mycoplasma spp., Borrelia spp. and Helicobacter pylori.
The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information provides only an approximate guidance on the probability of an organism being susceptible to azithromycin.
Table: Antibacterial spectrum of azithromycin

Commonly susceptible species
Aerobic Gram-negative
Haemophilus influenzae Moraxella catarrhalis Neisseria gonorrhoeae
Other microorganisms
Chlamydophila pneumoniae Chlamydia trachomatis Legionella spp. Mycobacterium avium Mycoplasma pneumoniae
Species for which acquired resistance may be a problem.
Aerobic Gram-positive
Staphylococcus aureus (methicillin-susceptible) Streptococcus pneumoniae Streptococcus pyogenes (erythromycin-intermediate)
Others
Ureaplasma urealyticum
Inherently resistant organisms
Aerobic Gram-positive
Staphylococci MRSA, MRSE

Aerobic Gram-negative
Escherichia coli Klebsiella spp. Pseudomonas aeruginosa
Anaerobic
Bacteroides fragilis group

° At the time of publication there are no current data. In primary literature, standard works and treatment guidelines susceptibility is assumed.

1 Resistance rate in some studies ≥10%

"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:

Following oral administration, the bioavailability of azithromycin is approximately 37 %. Peak plasma levels are reached after 2-3 hours. The mean maximum concentration observed (Cmax) after a single dose of 500 mg is approximately 0.4 µg/ml.

Distribution:

Orally administered azithromycin is widely distributed over the whole body.

Pharmacokinetic studies have shown considerably higher azithromycin concentrations in the tissues (up to 50 times the maximum concentration observed in the plasma) than in the plasma. This indicates that the substance is extensively bound in the tissues (steady-state volume of distribution approximately 31 l/kg).

With the recommended dosage no accumulation in the serum/plasma occurs. Accumulation does occur in the tissues where the levels are much higher than in the serum/plasma. Concentrations in target tissues such as lung, tonsil, and prostate exceed the MIC90 for likely pathogens after a single dose of 500 mg.

In experimental in-vitro and in-vivo studies, azithromycin accumulates in phagocytes; release is promoted by active phagocytosis. In animal models this process appeared to contribute to the accumulation of azithromycin in tissue. The binding of azithromycin to plasma proteins is variable, and varies from 52 % at 0.05 µg/ml to 18 % at 0.5 µg/ml, depending on the serum concentration.

Metabolism and Excretion:

The terminal plasma elimination half-life follows the tissue depletion half-life of 2 to 4 days.

Approximately 12 % of an intravenously administered dose is excreted in unchanged form with the urine over a period of 3 days; the major proportion in the first 24 hours. Concentrations of up to 237 µg/ml azithromycin, 2 days after a 5-day course of treatment, have been found in human bile. Ten metabolites have been identified (formed by N- and O-demethylation, by hydroxylation of the desosamine and aglycone rings, and by splitting of the cladinose conjugate). Investigations suggests that the metabolites do not play a role in the microbiological activity of azithromycin.

<u>Pharmacokinetics in Special populations:</u>

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.
Infants, toddlers, children and adolescents:
Pharmacokinetics have been studied in children aged 4 months – 15 years taking capsules, granules or suspension. At 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5, the Cmax achieved is slightly lower than adults with 224ug/l in children aged 0.6-5 years and after 3 days dosing and 383ug/l in those aged 6-15 years. The half-life of 36 h in the older children was within the expected range for adults.

5.3 Preclinical Safety Data
In animal studies using exposures 40 times those achieved at the clinical therapeutic dosages, azithromycin was found to have caused reversible phospholipidosis, but as a rule there were no associated toxicological consequences. The relevance of this finding to humans receiving azithromycin in accordance with the recommendations 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:
No teratogenic effects were observed in embryotoxicity studies in rats after oral administration of azithromycin. In rats, azithromycin dosages of 100 and 200 mg/kg bodyweight/day led to mild retardations in foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardations following treatment with 50 mg/kg/day azithromycin and above were observed.

6.0 Pharmaceutical Particulars

6.1 List of Excipients

Excipients: Lactose BP, Microcrystalline Cellulose BP, Maize starch BP, Povidone K-30 BP, Purified Talc BP, Magnesium Stearate BP, Colloidal Anhydrous Silica BP, Sodium Starch Glycolate (Type A) BP, Purified Water BP, Hypromellose (E-15) BP, Titanium Dioxide BP, Purified Talc BP, Macrogol 6000 BP, Colour Ponceau 4R Lake, Isopropyl Alcohol BP, Dichloromethane BP.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months from the date of manufacture.

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C in a dry place. Protect from light. Keep out of reach of children.

6.5 Nature and contents of container

1X3 X10 Blister Pack - 10 blister cards (each having 3 tablets) are packed in a secondary carton

(1X3) X10 Blister Pack - Single Blister card (having 3 tablets) is packed in a monocarton. Ten such monocarton are packed in a tertiary carton

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

MEDICAMEN Biotech Limited

SP-1192 A&B, PHASE - IV,

Industrial Area,

Bhiwadi - 301 019

Distt. Alwar,

Rajasthan, India.

8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

Registration No; 3311/3107/NMR/2017

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Approval date; 21-06-2017

10. DATE OF REVISION OF THE TEXT

July 2024