SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Swazi 250 (Azithromycin Tablets 250mg)
Swazi 500 (Azithromycin Tablets 500mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Swazi 250 (Azithromycin Tablets 250mg)
Each film coated tablet contains
Azithromycin USP (as dihydrate)
Equivalent to Azithromycin Anhydrous 250mg
Colour :Titanium Dioxide

Swazi 500 (Azithromycin Tablets 500mg)
Each film coated tablet contains
Azithromycin USP (as dihydrate)
Equivalent to Azithromycin Anhydrous 500mg
Colour: Titanium Dioxide

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film Coated tablet.

Swazi 250 (Azithromycin Tablets 250mg)
White colored, round shaped, biconvex, film coated tablets with both sides plain.

Swazi 500 (Azithromycin Tablets 500mg)
White colored, oblong shaped, biconvex, film coated tablets with both sides plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Azithromycin is indicated for the treatment of the following infections, when caused by microorganisms sensitive to Azithromycin:

- Acute bacterial sinusitis (adequately diagnosed)
- Acute bacterial otitis media (adequately diagnosed)
- Pharyngitis, tonsillitis
- Acute exacerbation of chronic bronchitis (adequately diagnosed)
- Mild to moderately severe community-acquired pneumonia
- Skin and soft tissue infections
- Uncomplicated *Chlamydia trachomatis* urethritis and cervicitis

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and Method of Administration

Adults

In uncomplicated *Chlamydia trachomatis* urethritis and cervicitis the dosage is 1000 mg as a single oral dose.

For all other indications the dose is 1500 mg, to be administered as 500 mg per day for three consecutive days. As an alternative the same total dose (1500 mg) can also be administered over a period of five days with 500 mg on the first day and 250 mg on the second to the fifth day.

Elderly people

The same dose range as in younger patients may be used in the elderly people. Since elderly people can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes.

Older People

The same dose range as in younger patients may be used in the elderly.

Paediatric population

Azithromycin tablets should only be administered to children weighing more than 45 kg when normal adult dose should be used. For children under 45 kg other pharmaceutical forms of azithromycin, e.g. suspensions, may be used.

Patients with renal impairment

No dose adjustment is necessary 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 <10ml/min).

Patients with hepatic impairment

A dose adjustment is not necessary for patients with mild to moderately impaired liver function (see section 4.4 and 5.2).

Method of administration

Azithromycin tablets should be given as a single daily dose. The tablets may be taken without regard to food.

4.3 Contra-indications

The use of azithromycin is contraindicated in patients with hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipients.

4.4 Special Warnings and Precautions for Use

Hypersenstivity

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

Cardiovascular events
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. Therefore as the following situations may lead to an increased risk for ventricular arrhytmias (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 older people) such as patients:
- With congenital or documented acquired QT prolongation.
- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of classes IA (quinidine and procainamide) and 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 hypomagnesaemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including azithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing azithromycin.

Clostridium difficile associated diarrhoea (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 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 two months after the administration of antimicrobial agents. In case of CDAD anti-peristaltics are contraindicated.

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy.
Safety and efficacy for the prevention or treatment of MAC in children have not been established.

The following should be considered before prescribing Azithromycin Tablets:
Azithromycin Tablets are not suitable for treatment of severe infections where a high concentration of the antibiotic in the blood is rapidly needed.
Azithromycin Tablets is not the first choice for the empiric treatment of infections in areas where the prevalence of resistant isolates is 10% or more.
In areas with a high incidence of erythromycin a resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to azithromycin and other antibiotics.
As for other macrolides, high resistance rates of Streptococcus pneumoniae (> 30 %) have been reported for azithromycin in some European countries. This should be taken into account when treating infections caused by Streptococcus pneumoniae.

Pharyngitis/ tonsillitis
Azithromycin Tablets are 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.

Sinusitis
Often, Azithromycin Tablets are not the substance of first choice for the treatment of sinusitis.

Acute otitis media
Often, Azithromycin Tablets are not the substance of first choice for the treatment of acute otitis media.

Skin and soft tissue infections
The main causative agent of soft tissue infections, Staphylococcus aureus, is frequently resistant to azithromycin. Therefore, susceptibility testing is considered a precondition for treatment of soft tissue infections with azithromycin.

Infected burn wounds
Azithromycin Tablets are not indicated for the treatment of infected burn wounds.

Sexually transmitted disease

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

Neurological or psychiatric diseases
Azithromycin Tablets should be used with caution in patients with neurological or psychiatric disorders.
As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms, including fungi is recommended.
In patients with severe renal impairment (GFR < 10 ml/min) a 33% increase in systemic exposure to azithromycin was observed.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Effects of other medicinal products on azithromycin:
Antacids
Simultaneously administration of antacids in the pharmacokinetics of azithromycin, no overall change has been observed in the bioavailability, although the peak concentrations of azithromycin measured in the plasma reduced by approximately 25%. In patients receiving both azithromycin and antacids, the medicinal products should not be taken simultaneously. Azithromycin Tablets should be taken at least 1 hour before or 2 hours after the antacids.

Astemizole, Alfentanil
No data are available on interactions with Astemizole 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.

Cetirizine
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)
Coadministration of daily doses of 1200 mg azithromycin with daily dose 400mg of didanosine in 6 HIV-positive subjects did not appear to affect the pharmakokinetics of didanosine as compared with placebo.

Digoxin and colchicine (P-gp 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-gp substrates such as digoxin are administered concomitantly, the possibility of elevated serum concentrations of the substrate should be considered.

Zidovudine
1000 mg single doses and 1200 mg or 600 mg multiple doses of azithromycin had little effect upon the pharmacokinetics of zidovudine or its glucuronide metabolite in the plasma or upon excretion in urine. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in mononuclear cells in the

peripheral circulation. 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.

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

Ergotamine derivatives
Due to the theoretical possibility of ergotism, the concurrent use of azithromycin and ergot derivatives is not recommended.

Pharmacokinetic studies have been conducted between azithromycin and the following drugs known to undergo significant cytochrome P450 mediated metabolism.

Atorvastatin
Coadministration 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
No significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.

Cimetidine
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
Azithromycin does 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.

Cyclosporine
After administration of 500 mg/day oral dose of azithromycin for 3 days and then a single 10 mg/kg oral dose of cyclosporine, the resulting cyclosporine Cmax and AUC_{0-5} 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, cyclosporine 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 pharmacokinetlc 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.

Indinavir
Coadministration 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
Azithromycin has no significant effect on the pharmacokinetics of methylprednisolone.

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.

Nelfinavir
Concomitant administration of 1200 mg azithromycin and steady state nelfinavir (750 mg 3 times daily) resulted in increase of azithromycin concentrations. No dose adjustment is necessary but patients should be monitored for known side effects of azithromycin.

Rifabutin
Coadministration 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.

Sildenafil
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.

Theophylline
There is no evidence of a clinically significant pharmacokinetic interaction when azithromycin and theophylline are coadministered to healthy volunteers. As interactions of other macrolides

with theophylline have been reported, alertness to signs that indicate a rise in theophylline levels is advised.

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.

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 Fertility, 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. 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.

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. It is recommended to discard the milk during treatment and up until 2 days after discontinuation of treatment. Nursing may be resumed thereafter.

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
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
The frequency grouping is defined using the following convention:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,1000 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.

Infections and infestations:
Uncommon: Candidiasis, pneumonia, fungal infection, bacterial infection, pharyngitis, gastroenteritis, respiratory disorder, rhinitis, oral candidiasis, vaginal infection
Not known: Pseudomembranous colitis

Blood and lymphatic system disorders:
Uncommon: Leukopenia, neutropenia, Eosinophilia
Not Known: Thrombocytopenia, haemolytic anaemia

Immune system disorders:
Uncommon: Angioderma, hypersensitivity
Not known: Anaphylactic reaction

Metabolism and nutrition disorders:
Uncommon: Anorexia
Psychiatric disorders:
Uncommon: Nervousness, Insomnia
Rare: Agitation, depersonalisation
Not known: Aggression, anxiety, delirium, hallucination

Nervous system disorders:
Common: Headache
Uncommon: Dizziness, dysgeusia, paresthesia, somnolence,
Not known: Hypoaesthesia, Syncope, convulsion, psychomotor, hyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis

Eye disorders:
Common: Visual impairment
Not known: Blurred vision

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

Cardiac disorders:
Uncommon: Palpitations
Not known: Torsades de pointes, arrhythmia including ventricular tachycardia, electrocardiogram QT prolonged

Vascular disorders:
Uncommon: Hot flush
Not known: Hypotension

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

Gastrointestinal disorders:
Very common: Diarrhea
Common: Vomiting, abdominal pain, nausea, dyspepsia
Uncommon: Gastritis, constipation, flatulence, dyspepsia, Dysphagia, abdominal distension, dry mouth, eructation, mouth ulceration, salivary hypersecretion
Not known: Pancreatitis, tongue discolouration

Hepatobiliary disorders:
Uncommon: Hepatitis
Rare: Hepatic function abnormal, jaundice cholestatic
Not known: Hepatic failure (which has rarely resulted in death), hepatitis fulminant, hepatic necrosis

Skin and subcutaneous tissue disorders:
Uncommon: Rash, pruritus, dermatitis, dry skin, hyperhidrosis, urticaria
Rare; Photosensitivity reaction, acute generalised exanthematous pustulosis (AGEP)
Not known: Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme

Musculoskeletal and connective tissue disorders:
Uncommon: Osteoarthritis, myalgia, back pain, neck pain
Not Known**:** Arthralgia

Renal and urinary disorders:
Uncommon: Blood urea increased Dysuria, renal pain
Not Known: Renal failure acute, nephritis interstitial

Reproductive system and breast disorders:
Uncommon***:*** Metrorrhagia, testicular disorder

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

Investigations:
Common: Blood bicarbonate decreased Lymphocyte count decreased, eosinophil count increased, basophils increased, monocytes increased, neutrophils increased
Uncommon: Blood creatinine increased, blood potassium abnormal Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood bilirubin increased, blood urea increased, blood alkaline phosphatase increased, chloride increased, glucose increased, platelets increased, hematocrit decreased, bicarbonate increased, abnormal sodium

Injury and poisoning:

Uncommon: post procedural complication

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.

4.9. Overdose
The adverse events experienced in higher than recommended dosages were similar to those seen at normal doses. The typical symptoms of an overdose with macrolide antibiotic include reversible loss of hearing, severe nausea, vomiting and diarrhea. In the event of overdosage, general symptomatic and supportive measures are indicated as required.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamics Properties

General properties
Pharmacotherapeutic group: antibacterials for systemic use; macrolids; azithromycin, ATC code: J01FA10

Mode of action
Azithromycin is an azalide, a sub-class of the macrolid antibiotics. The mechanism of action of azithromycin is based on the suppression of bacterial protein synthesis, that is to say that it binds to the ribosomal 50s sub-unit and inhibits the translocation of peptides. Azithromycin acts bacteriostatic.

PK/PD Relationship
The efficacy of azithromycin is best described by the relationship AUC/MIC, where AUC describes the area under the curve and MIC represents the mean inhibitory concentration of the microbe concerned.

Mechanism of resistance
Resistance to azithromycin may be natural or acquired. There are 3 main mechanisms of resistance affecting azithromycin:
- Efflux: resistance may be due to an increase in the number of efflux pumps on the cell membrane. In particular, 14- and 15-link macrolides are affected. (M-phenotype)- Alterations of the cell structure: methylisation of the 23s rRNS may reduce the affinity of the ribosomal binding sites, which can result in microbial resistance to macrolides, Lincosamides and group B streptogramins (SB) (MLSB-phenotype).
- Enzymatic deactivation of macrolides is only of limited clinical significance.
In the presence of the M-phenotype, complete cross resistance exists between azithromycin and clarithomycin, erythromycin and roxithromycin. With the MLSB-phenotype, additional cross resistance exists with clindamycin and streptogramin B. A partial cross resistance exists with spiramycin.

Susceptibility

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.

Commonly susceptible species

Aerobic Gram-negative microorganisms

*Haemophilus influenzae**
*Moraxella catarrhalis**
Neisseria gonorrhoeae

Other microorganisms

Chlamydophila pneumoniae
Chlamydia trachomatis
Legionella pneumophila
Mycobacterium avium
*Mycoplasma pneumonia**

Species for which acquired resistance may be a problem

Aerobic Gram-positive microorganisms

*Staphylococcus aureus**
*Streptococcus agalactiae**
*Streptococcus pneumoniae**
*Streptococcus pyogenes**

Aerobic Gram-negative microorganisms

Escherichia coli
Klebsiella spp.
Pseudomonas aeruginosa

Other microorganisms

Ureaplasma urealyticum

Inherently resistant organisms

Aerobic Gram-negative microorganisms

Staphylococcus aureus- methicillin resistant and erythromycin resistant strains
Streptococcus pneumoniae- penicillin resistant strains
Escherichia coli
Pseudomonas aeruginosa
Klebsiella spp.

Anerobic Gram-negative microorganisms

Bacteroides fragilis group

*Clinical effectiveness is demonstrated by sensitive isolated organisms for approved clinical indication.

5.2 Pharmacokinetic properties:

Absorption
After oral administration the bioavailability of azithromycin is approximately 37%. Peak plasma levels are reached after 2-3 hours (C_{max} after a single dose of 500 mg orally was approximately 0.4 mg/l).

Distribution
Kinetic studies have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the active substance is heavily tissue bound (steady state distribution volume of approximately 31 l/kg).Concentrations in target tissues such as lung, tonsil, and prostate exceed the MIC90 for likely pathogens after a single dose of 500 mg. In serum the protein binding of azithromycin is variable and depending on the serum concentration varies from 50% in 0.05 mg/l to 12% in 0.5 mg/l.
In experimental in vitro and in vivo studies azithromycin accumulates in the phagocytes, freeing is stimulated by active phagocytosis. In animal studies this process appeared to contribute to the accumulation of azithromycin in the tissue.

Elimination
Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. About 12% of an intravenously administered dose is excreted in the urine unchanged
over a period of 3 days; the majority in the first 24 hours. Biliary excretion of azithromycin, predominantly in unchangedform, is a major route of elimination.
The identified metabolites (formed by N- and O- demethylising, by hydroxylising of the desosamine and aglycone rings, and by the splitting of the cladinose conjugate) are microbiologically inactive.
After a 5 day treatment slightly higher (29%) AUC values were seen in the elderly volunteers (>65 years of age) compared to the younger volunteers (< 45 years of age). However these differences are not regarded as clinically relevant; therefore a dose adjustment is not recommended.
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 than are released from inactive phagocytes. In animal models the azithromycin concentrations measured in inflammation foci were high.

Pharmacokinetics in special populations:
Renal insufficiency
Following a single oral dose of azithromycin 1 g, mean C_{max} and AUC_{0-120} 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> 80 ml/min). In subjects with severe renal impairment, the mean C_{max} and AUC_{0-120} increased 61% and 33% 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.

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 C_{max} achieved is slightly lower than adults with 224 ug/l in children aged 0.6-5 years and after 3 days dosing and 383 ug/l in those aged 6-15 years. The $t_{1/2}$ of 36 h in the older children was within the expected range for adults.

5.3 Preclinical Safety Data

In high-dose animal studies, giving active substance concentrations 40 fold higher than those expected in clinical practice, azithromycin has been noted to cause reversible phospholipidosis, generally without discemible toxicological consequences. There is no evidence that this is of relevance to the normal use of azithromycin in humans.

Carcinogenic potential:
Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Mutagenic potential:
Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay.

Reproductive toxicity:
No teratogenic effects were observed in animal studies of embryotoxicity in mice and rats. 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 pre-/postnatal studies in rats, mild retardations following treatment with 50 mg/kg/day azithromycin and above were observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

For Core Tablet
Dibasic Calcium Phosphate (Dihydrate)
Pregelatinized Starch
Croscarmellose Sodium
Sodium Lauryl Sulphate
Maize Starch
Magnesium Stearate

Film coat
Opadry II White 31G58920 consisting of Hypromellose, Lactose Monohydrate, Titanium Dioxide, Macrogol/ Polyethylene Glycol and Talc.

6.2 Incompatibilities
Not applicable.

6.3 Shelf Life
36 Months

6.4 Special Precautions for Storage
Store below 30°C. Protect from light and moisture.

6.5 Nature and Contents of Container

Azithromycin Tablets 250mg: Blister pack of 6 tablets using Rigid PVC film coated with clear PVdC and Printed Aluminium Foil.

Azithromycin Tablets 500mg: Blister pack of 3 tablets using Rigid PVC film coated with clear PVdC and Printed Aluminium Foil.

6.6 Special precautions for disposal

No special requirements

Administrative Data

7. MARKETING AUTHORISATION HOLDER
IND-SWIFT LIMITED
Off. NH-21, Village Jawaharpur,
Tehsil Derabassi, District SAS Nagar (Mohali),
Punjab-140507, India.
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8. MARKETING AUTHORISATION NUMBER
Swazi 250- 05134/07062/REN/2019
Swazi 500- 05135/07061/REN/2019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION
Swazi 250- Date of first authorisation:- 06.06.2015
Date of latest renewal:- 12.05.2020

Swazi 500- Date of first authorisation:- 06.06.2015
Date of latest renewal:- 12.05.2020

10. DATE OF (PARTIAL) REVISION OF THE TEXT
July 2023.