Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Fast Kit
(Azithromycin (As dihydrate) 1000mg, Fluconazole 150mg, and Secnidazole 1000mg, Combi Kit)

2. Qualitative and quantitative composition

Each kit contains:
Azithromycin (as Dihydrate) 1000mg,
Fluconazole 150mg,
Secnidazole 1000mg.

For a full list of excipients, see section 6.1

3. Pharmaceutical form

Azithromycin: White coloured caplet shaped tablet
Fluconazole: Pink Coloured caplet, plain on one side and scored on the other side.
Secnidazole: Yellow coloured caplet shaped tablet.

4. Clinical particulars

4.1 Therapeutic indications

FAST KIT TABLETS is indicated for treatment of mixed vaginal infections or as empirical cure of suspected mixed vaginal infections such as vulvovaginitis, bacterial vaginosis and trichomoniasis; it is also indicated in syndromic management of pelvic inflammatory disease.

4.2 Posology and method of administration

Adults: Azithromycin 1g tablet as a single oral dose. Fluconazole 150mg orally as a single dose. Secnidazole 2g single dose (administration of 2 Secnidazole 1g tablets).

The absorption of Azithromycin is hampered by presence of food in the stomach. Hence Azithromycin to be administered 1 hour before meals. Fluconazole, administration is not hampered by presence of food. 1 tablet of fluconazole to be administered after lunch. 2 tablets of Secnidazole to be administered after food preferably at bed time. This shall avoid any Gastro-intestinal disturbances.

4.3 Contraindications

Azithromycin

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

Fluconazole

Hypersensitivity to fluconazole or to any excipients listed in section 6.1. There is no information regarding cross hypersensitivity between fluconazole and other azole antifungal agents, use with caution in patients with hypersensitivity to other azoles.

Co-administration with terfenadine or cisapride is contra-indicated in patients receiving fluconazole. *See 'Interactions with other medicinal products and other forms of interaction'.*

Secnidazole
As in case of other nitroimidazole derivatives, the drug should not administered during the first trimester of pregnancy, or lactation or in individuals hypersensitive to nitroimidazole derivatives.

4.4 Special warnings and precautions for use

Azithromycin:

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.

Fluconazole:
In some patients, especially those with serious underlying diseases such as AIDS and cancer, abnormalities in haematological, hepatic, renal and other biochemical function test results have been observed during treatment with fluconazole but the clinical significance and relationship to treatment is uncertain.

Very rarely, patients who died with severe underlying disease and who had received multiple doses of fluconazole had post-mortem finding which included hepatic necrosis.

These patients were receiving multiple concomitant medications, some known to be potentially hepatotoxic, and/ or had underlying diseases which could have caused the hepatic necrosis.

In cases of hepatotoxicity, no obvious relationship to total daily dose of fluconazole, duration of therapy, sex or age of the patient has been observed; the abnormalities have usually been reversible on discontinuation of fluconazole therapy.

Since a causal relationship with fluconazole cannot be excluded, patients who develop abnormal liver function tests during fluconazole therapy should be monitored for the development of more serious hepatic damage. Fluconazole should be discontinued if clinical signs or symptoms consistent with liver disease develop during treatment with fluconazole.

Patients have occasionally developed exfoliative cutaneous reactions, such as Stevens-Johnson Syndrome and toxic epidermal necrolysis, during treatment with fluconazole. AIDS patients are more prone to the development of more severe cutaneous reactions to many drugs.

If a rash develops in a patient treated for a superficial fungal infection which may be attributed to fluconazole, further therapy with this agent should be discontinued. If patients with invasive/ systemic fungal infections develop

rashes, they should be monitored closely and fluconazole discontinued if bullous lesions or erythema multiforme develop.
In rare cases, as with other azoles, anaphylaxis has been reported.

Secnidazole:

As with related compounds, alcoholic beverages should be avoided during Secnidazole therapy because of the possibility of a disulfiram-like reaction (flushing, abdominal cramps, vomiting, tachycardia). Alcohol should be avoided until 72 hours after discontinuing Secnidazole.

4.5 Interaction with other medicinal products and other forms of interaction

Azithromycin:

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

Fluconazole:

The following drug interactions relate to the use of multiple-dose fluconazole, and the relevance to single-dose fluconazole has not yet been established:

Anticoagulants In an interaction study, fluconazole increased the prothrombin time (12%) after warfarin administration in healthy males. In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, haematuria and melaena) have been reported in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. Prothrombin time in patients receiving coumarin-type anticoagulants should be carefully monitored.

Benzodiazepines (Short acting) Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. This effect on midazolam appears to be more pronounced following oral administration of fluconazole than with fluconazole administered intravenously. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dosage and the patients should be appropriately monitored.

Sulphonylureas Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulphonylureas (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Fluconazole and oral sulphonylureas may be co-administered to diabetic patients, but the possibility of a hypoglycaemic episode should be borne in mind.

Hydrochlorothiazide In a kinetic interaction study, co-administration of multiple-dose hydrochlorothiazide to healthy volunteers receiving fluconazole increased plasma concentrations of fluconazole by 40%. An effect of this magnitude should not necessitate a change in the fluconazole dose regimen in subjects receiving concomitant diuretics, although the prescriber should bear it in mind.

Phenytoin Concomitant administration of fluconazole and phenytoin may increase the levels of phenytoin to a clinically significant degree. If it is necessary to administer both drugs concomitantly, phenytoin levels should be monitored and the phenytoin dose adjusted to maintain therapeutic levels.

Oral contraceptives Two kinetic studies with combined oral contraceptives have been performed using multiple doses of fluconazole. There were no relevant effects on either hormone level in the 50 mg fluconazole study, while at 200 mg daily the AUCs of ethinylestradiol and levonorgestrel were increased 40% and 24% respectively. Thus multiple dose use of fluconazole at these levels is unlikely to have an effect on the efficacy of the combined oral contraceptive.

Rifampicin Concomitant administration of fluconazole and rifampicin resulted in a 25% decrease in the AUC and 20% shorter half-life of fluconazole. In patients receiving concomitant rifampicin, an increase in the fluconazole dose should be considered.

Endogenous steroid Fluconazole 50mg daily does not affect endogenous steroid levels in females: 200 – 400 mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers.

Ciclosporin A kinetic study in renal transplant patients found fluconazole 200 mg daily to slowly increase ciclosporin concentrations. However, in another multiple dose study with 100 mg daily, fluconazole did not affect ciclosporin levels in patients with bone marrow transplants. Ciclosporin plasma concentration monitoring in patients receiving fluconazole is recommended.

Theophylline In a placebo controlled interaction study, the administration of fluconazole 200 mg for 14 days resulted in an 18 % decrease in the mean plasma clearance of theophylline. Patients who are receiving high doses of theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole, and the therapy modified if signs of toxicity develop.

Terfenadine Because of the occurrence of serious dysrhythmias secondary to prolongation of the QTc interval in patients receiving other azole antifungals in conjunction with terfenadine, interaction studies have been performed. One study at a daily dose of 200 mg of fluconazole failed to demonstrate a prolonged QTc interval. Another study at a 400 mg and 800 mg daily dose of fluconazole demonstrated that fluconazole taken in multiple doses of 400 mg per day or greater did significantly increase plasma levels of terfenadine when taken concomitantly.

There have been spontaneously reported cases of palpitations, tachycardia, dizziness, and chest pain in patients taking concomitant fluconazole and terfenadine where the relationship of the reported adverse events to drug therapy or underlying medical conditions was unclear. Because of the potential seriousness of such an interaction, it is recommended that terfenadine should not be taken in combination with fluconazole. *See 'Contraindications'.*

Cisapride There have been reports of cardiac events including torsade de pointes in patients to whom fluconazole and cisapride were co-administered. In most of these cases, the patients appear to have been predisposed to arrhythmias or had serious underlying illnesses, and the relationship of the reported events to a possible fluconazole-cisapride drug interaction is unclear. Because of the potential seriousness of such an interaction, co-administration of cisapride is contra-indicated in patients receiving fluconazole. *(See 'Contraindications'.)*

Zidovudine Two kinetic studies resulted in increased levels of zidovudine most likely caused by the decreased conversion of zidovudine to its major metabolite. One study determined zidovudine levels in AIDS or ARC patients before and following fluconazole 200 mg daily for 15 days. There was a significant increase in zidovudine AUC (20 %). A second randomised, two-period, two-treatment cross-over study examined zidovudine levels in HIV infected patients. On two occasions, 21 days apart, patients received zidovudine 200 mg every eight hours either with or without fluconazole 400 mg daily for seven days. The AUC of

zidovudine significantly increased (74 %) during co- administration with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions.

Rifabutin There have been reports that an interaction exists when fluconazole is administered with rifabutin, leading to increased serum levels of rifabutin. There have been reports of uveitis in patients to whom fluconazole and rifabutin were co-administered. Patients receiving the two concomitantly should be carefully monitored.

Tacrolimus There have been reports of an interaction when fluconazole is given concomitantly with tacrolimus, leading to increased serum levels of tacrolimus. There have been reports of nephrotoxicity in patients to whom fluconazole and tacrolimus were co-administered. Patients receiving the two concomitantly should be carefully monitored.

The use of fluconazole in patients concurrently taking astemizole, rifabutin, tacrolimus, or other drugs metabolised by the cytochrome P450 system may be associated with elevations in serum levels of these drugs. In the absence of definitive information, caution should be used when co-administering fluconazole. Patients should be carefully monitored.

Interaction studies have shown that when oral fluconazole is co-administered with food, cimetidine, antacids or following total body irradiation for bone marrow transplantation, no clinically significant impairment of fluconazole absorption occurs.

Physicians should be aware that drug-drug interaction studies with other medications have not been conducted, but that such interactions may occur.

Secnidazole:

Alcohol: Concurrent use of Secnidazole and alcohol may produce a disulfiram-like reaction and should be avoided.

4.6 Pregnancy and Lactation

Azithromycin:

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.

Fluconazole:

Use during pregnancy:

There are no adequate and well controlled studies in pregnant women. There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400 – 800 mg/ day) fluconazole therapy for coccidioidomycosis. The relationship between fluconazole and these events isunclear. Accordingly, fluconazole capsules should not be used in pregnancy or in women of childbearing potential, unless adequate contraception is employed.

Use during lactation:

Fluconazole is found in human breast milk at concentrations similar to plasma, hence its use in nursing mothers is not recommended.

Secnidazole:

Pregnancy

Animal studies have shown reproductive toxicity. Secnidazole crosses the placental barrier. Since the effects of compounds of this class on foetal development are unknown, Secnidazole is contraindicated in the first trimester of pregnancy.
There is no evidence that Secnidazole is harmful during the latter stages of pregnancy, but it should be used in the second and third trimesters only in cases where it is absolutely necessary, when the benefits of therapy outweigh possible risks to both mother and foetus.

Breast-feeding

Secnidazole is excreted in breast milk. Secnidazole may continue to appear in

breast milk for more than 72hours after administration. Women should not nurse until at least 3 days after having discontinued taking Secnidazole.

Fertility

There are no human data on the effect of Secnidazole on fertility. Male and female fertility may be impacted

4.7 Effects on ability to drive and use machines

There is no evidence to suggest that Azithromycin, Fluconazole and Secnidazole may have an effect on a patient's ability to drive or operate machinery.

For secnidazole, no special precautions should be necessary. However, drugs of similar chemical structure, including Secnidazole,have been associated with various neurological disturbances such as dizziness, vertigo, ataxia, peripheral neuropathy (paraesthesia, sensory disturbances, hypoaesthesia) and rarely convulsions. If any abnormal neurological signs develop during Secnidazole therapy, the drug should be discontinued.

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:

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 Infestatio			Candidiasis Vaginal infection Pneumonia Fungal infection			Pseudomembrano -us colitis (see

ns			Bacterial infection Pharyngitis Gastroenteritis Respiratory disorder Rhinitis Oral candidiasis			section 4.4)
Blood and Lymphatic System Disorders			Leukopenia Neutropenia Eosinophilia			ThrombocytopeniaHaemolytic 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 reaction		SJS, TEN Erythema multiforme
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 pain Nausea Flatulence Abdominal discomfort Loose 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

Fluconazole:

Fluconazole is generally well tolerated. The most common side effects observed during clinical trials and associated with fluconazole are:

Nervous System Disorders:
Headache.

Skin and Subcutaneous Tissue Disorders:
Rash.

Gastrointestinal Disorders:
Abdominal pain, diarrhoea, flatulence, nausea.

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, changes in renal and haematological function test results and hepatic abnormalities have been observed during treatment with fluconazole and comparative agents, but the clinical significance and relationship to treatment is uncertain *(see 4.4 Special warnings and special precautions for use).*

Hepatobiliary Disorders:

Hepatic toxicity including rare cases of fatalities, elevated alkaline phosphatase, elevated bilirubin, elevated SGOT, elevated SGPT.

In addition, the following undesirable effects have occurred during post-marketing:
Nervous System Disorders: Dizziness, seizures, taste perversion.

Skin and Subcutaneous Tissue Disorders:
Alopecia, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Gastrointestinal Disorders:
Dyspepsia, vomiting.

Blood and Lymphatic Disorders:
Leukopenia including neutropenia and agranulocytosis, thrombocytopenia.

Immune System Disorders:
Allergic reaction: anaphylaxis (including angio-oedema, face oedema, pruritus), urticaria.

Hepatobiliary Disorders: Hepatic failure, hepatitis, hepatocellular necrosis, jaundice.

Metabolism and Nutrition Disorders:
Hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia.

Secnidazole

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The safety data described below reflect exposure to 589 patients, of whom 518 received a 2 g dose of SECNIDAZOLE. SECNIDAZOLE was evaluated in three clinical trials of patients diagnosed with bacterial vaginosis: two placebo-controlled trials (Trial 1 n=215, Trial 2 n=189) and one uncontrolled safety trial (Trial 3 n=321).
All patients received a single oral dose of study medication or placebo. Trial 1 evaluated a 1 g (this dose is not approved) dose (n=71) and a 2 g dose (n=72) of SECNIDAZOLE. Trial 2 evaluated a 2 g dose (n=125). The population was female, aged 15 to 54 years. Patients in the placebo-controlled trials were primarily Black or African American (54%) or Caucasian (41%).
There were no deaths in the trials. Two patients in Trial 3 discontinued due to vulvovaginal candidiasis in the SECNIDAZOLE-treated arm.
Most Common Adverse Reactions

Among 197 patients treated with a single 2 g dose of SECNIDAZOLE in the two placebo-controlled trials, Trial 1 and 2, adverse reactions were reported by approximately 29% of patients. Table 1 displays the most common adverse reactions (≥ 2 % in SECNIDAZOLE-treated patients) in these two trials.

4.9 Overdose

Azithromycin:

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.

Fluconazole:

There have been reports of overdose with fluconazole and hallucination and paranoid behaviour have been concomitantly reported.
In the event of overdose, symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate.
Fluconazole is largely excreted in the urine, forced volume diuresis would probably increase the elimination rate. A three-hour hemodialysis session decreases plasma levels by approximately 50%.

Secnidazole:

Signs and symptoms of overdosage: There are no reported overdoses in humans with Secnidazole.
Treatment for overdosage: There is no specific antidote for treatment of overdosage with Secnidazole. Treatment is symptomatic and supportive. Gastric lavage may be useful. Secnidazole is easily dialysable.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Azithromycin:
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. The chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin A. The molecular weight is 749.0.

Mechanism of action
Azithromycin is an azalide, a sub-class of the macrolide antibiotics. By binding to the 50S ribosomal sub-unit, azithromycin avoids the translocation of peptide chains from one side of the ribosome to the other. As a consequence of this, RNA-dependent protein synthesis in sensitive organisms is prevented.

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

Mechanism of resistance:
Resistance to azithromycin may be inherent or acquired. There are three main mechanisms of resistance in bacteria: target site alteration, alteration in antibiotic transport and modification of the antibiotic.
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.
Complete cross resistance exists among *Streptococcus pneumoniae*, betahaemolytic streptococcus of group A, *Enterococcus faecalis* and *Staphylococcus aureus*, including methicillin resistant *S. aureus* (MRSA) to erythromycin, azithromycin, other macrolides and lincosamides.

Fluconazole:

ATC code: J02AC01.

Mechanism of action
Fluconazole is a triazole antifungal agent. Its primary mode of action is the inhibition of fungal cytochrome P-450- mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungalactivity of fluconazole. Fluconazole has been shown to be more selective for fungal cytochrome P- 450 enzymes than for various mammalian cytochrome P-450 enzyme systems.
Fluconazole 50 mg daily given up to 28 days has been shown not to effect testosterone plasma concentrations in males or steroid concentration in females of child-bearing age. Fluconazole 200 mg to 400 mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers. Interaction studies with antipyrine indicate that single or multiple doses of fluconazole 50 mg do not affect its metabolism.

Pharmacokinetic/pharmacodynamic relationship
Mechanisms of resistance
Candida spp have developed a number of resistance mechanisms to azole antifungal agents. Fungalstrains which have developed one or more of these resistance mechanisms are known to exhibit high minimum inhibitory concentrations (MICs) to fluconazole which impacts adversely efficacyin vivo and clinically.
There have been reports of superinfection with Candida species other than C. albicans, which are often inherently not susceptible to fluconazole (e.g. Candida krusei). Such cases may require alternative antifungal

therapy.

Secnidazole:

ATC code: J 01XD02
Secnidazole is active against both protozoa and obligate anaerobic bacteria. The activity against protozoa involves *Trichomonas vaginalis*, *Entamoeba histolytica* and *Giardia lamblia.*
The mode of action of Secnidazole against anaerobic bacteria and protozoa involves penetration of the drug into the cell of the micro-organism and subsequent damage of DNA strands or inhibition of their synthesis.
Secnidazole is active against *Helicobacter pylori*, *Gardnerella vaginalis* and most anaerobic bacteria including *Bacteroides fragilis*, *Bacteroides melaninogenicus*, Bacteroides spp., Clostridium spp., Eubacterium spp., Fusobacterium spp., Peptococcus spp., Peptostreptococcus spp. and Veillonella spp.
Helicobacter pylori (H.pylori) is associated with acid peptic disease including duodenal ulcer and gastric ulcerin which about 95% and 80% of patients respectively are infected with this agent. *H.pylori* is also implicated as a major contributing factor in the development of gastritis and ulcer recurrence in such patients. Evidence suggests a causative link between *H.pylori* and gastric carcinoma.
Clinical evidence has shown that the combination of Secnidazole with omeprazole and clarithromycin eradicates 91-96% of *H.pylori* isolates.

5.2 Pharmacokinetic properties

Azithromycin:
Absorption:
Bioavailability of azithromycin after oral administration is approximately 37%. Peak plasma concentrations are attained after 2-3 hours. The mean maximum concentration observed (C_{max}) after a single dose of 500 mg is approximately 0.4 µg/ml.
Distribution:
Orally administered azithromycin is widely distributed throughout the body.
Pharmacokinetic studies have demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (up to 50 times the maximum observed concentration in plasma) than those measured in plasma. This indicates that the agent strongly binds to tissues (steady-state distribution volume approx. 31 l/kg).
At the recommended dose no accumulation appears in the serum. Accumulation appears in tissues where levels are much higher than in serum. Three days after administration of 500 mg as a single dose or in partial doses concentrations of 1,3-4,8 µg/g, 0,6-2,3 µg/g, 2,0-2,8 µg/g and 0-0,3 µg/ml have been measured in resp. lung, prostate, tonsil and serum.
In experimental *in vitro* and *in vivo* studies azithromycin accumulates in

phagocytes. Release is stimulated by active phagocytosis. In animal models this process contributes to the accumulation ofazithromycin in tissue.
Binding of azithromycin to serum proteins is variable and varies from 50% at 0,05 mg/l to 18% at 0,5 mg/l, depending on the serum concentration.

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 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 suggest that the metabolites do not play a role in the microbiological activity of azithromycin.

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 of10-80 ml/min) compared with normal renal function (GFR > 80ml/min). In subjects with severe renal impairment, the mean C_{max} and AUC_{0-120} increased 61% and 33% respectively compared to normal.

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 have been measured after a 5 day treatment than in younger volunteers (< 45 years). These differences are not regarded as clinically relevant; dose adjustment is therefore not recommended.
Infants, toddlers, children and adolescents:
Pharmacokinetics has 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 25, the C_{max} achieved is slightly lower than in adults, with 224 µg/l in children aged 0.6-5 years and after 3 days dosing, and 383 µg/l in those aged 6-15 years. The half-life of 36 h in the older children was within the expected range for adults.

<u>Fluconazole:</u>
The pharmacokinetic properties of fluconazole are similar following administration by theintravenous or oral route.

Absorption
After oral administration fluconazole is well absorbed and plasma levels (and systemic bioavailability) are over 90% of the levels achieved after intravenous administration. Oral administration is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0.5 – 1.5 hours post-dose with a plasma elimination half-life ofapproximately 30 hours. Plasma concentrations are proportional to dose. Ninety percent steady- state levels are reached by day 4 – 5 with multiple once daily dosing.
The administration of a loading dose on the first day, double that of the normal daily dose, raises plasma levels to approximate to 90% steady-state levels by the second day.

Distribution
The apparent volume of distribution approximates to total body water. Plasma protein binding is low (11- 12%).
Fluconazole achieves good penetration in all body fluids studied. The levels of fluconazole in saliva and sputum are similar to plasma levels. In patients with fungal meningitis, fluconazole levels in the CSF are approximately 80% of the corresponding plasma levels.

Biotransformation
Fluconazole is metabolised only to a minor extent. Of a radioactive dose, only 11% is excreted in a changed form in the urine. Fluconazole is a selective inhibitor of the isozymes CYP2C9 and CYP3A4. Fluconazole is also an inhibitor of the isozyme CYP2C19.

Elimination
Plasma elimination half-life for fluconazole is approximately 30 hours. The major route of excretion is renal, with approximately 80% of the administered dose appearing in the urine as unchanged drug. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites.

Secnidazole:

Secnidazole is rapidly and completely absorbed following oral administration. In studies with healthy volunteers receiving 2g Secnidazole orally, peak serum levels of 40-51 micrograms/ml were achieved within two hours and decreased to between 11-19 micrograms/ml at 24 hours. Healthy volunteers who received 800mg and 1.6g Secnidazole IV over 10-15 minutes achieved peak plasma concentrations that ranged from 14 to 21mcg/ml for the 800mg dose and averaged
32mcg/ml for the 1.6g dose. At 24 hours postinfusion, plasma levels of Secnidazole decreased to
4-5mcg/ml and 8.6mcg/ml respectively, justifying once daily dosing.
Plasma levels decline slowly and Secnidazole can be detected in plasma

at concentrations of up to 1 microgram/ml at
72 hours after oral administration. The plasma elimination half-life for Secnidazole is between 12-14 hours.
Secnidazole is widely distributed in all body tissues and also crosses the blood brain barrier, obtaining clinically effective concentrations in all tissues. The apparent volume of distribution is about 50 litres. About 12% of plasma Secnidazole is bound to plasma protein.

Secnidazole is excreted by the liver and kidneys. Studies in healthy patients have shown that over 5 days, 60-65% of an administered dose is excreted by the kidneys with 20-25% of the administered dose excreted as unchanged Secnidazole. Up to 5% of the administered dose is excreted in the faeces.

Studies in patients with renal failure (creatinine clearance <22ml/min) indicate that there is no statistically significant change in Secnidazole pharmacokinetic parameters in these patients.

5.3 Preclinical safety data

Azithromycin:

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:
Teratogenic effects were not observed in rat reproductive toxicity studies. In rats, azithromycin doses of 100 and 200 mg/kg body weight/ day led to mild retardation in foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats mild retardations in physical and reflex development were noted following treatment with 50 mg/kg/day azithromycin and above.

Fluconazole:

Carcinogenesis: Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5 or 10 mg/kg/day (approximately 2-7 times the recommended human dose). Male rats treated with 5 and 10mg/kg/day had an increased incidence of hepatocellular adenomas.

Secnidazole:

Repeat-dose toxicity

In a repeat-dose toxicity study in beagle dogs, oral administration of Secnidazole increased atrophy of the thymus in both sexes at 300 and 600 mg/kg/day, and atrophy of the prostate in males at all doses of 100, 300 and 600 mg/kg/day. The initial highest dose of 1000 mg/kg/day was lowered to 600 mg/kg/day due to severe clinical signs. The no-observed-adverse-effect level for females was 100 mg/kg/day (approximately 0.9 times the highest human dose based upon plasma AUC).

6. Pharmaceutical Particulars

6.1 List of Excipients

Azithromycin:

Starch
Microcrystaline cellulose powder
Starch
Gelatine
Povidone K 30
Sodium Benzoate

Magnesium Stearate
Purified talc
Colloidal silicon dioxide
Cross Carmellose Sodium
Film Coating
HPMC
Talcum
Propylene Glycol
Titanium dioxide
Tartrazine Yellow
IPA
MDC
Colour Erythrosine

Fluconazole:

Starch
Microcrystaline cellulose powder
Gelatine
Povidone K 30
Sodium Benzoate
Magnesium Stearate
Purified talc
Colloidal silicon dioxide
Cross Carmellose Sodium
Film Coating
HPMC
Talcum
Propylene Glycol
Titanium dioxide

Tartrazine Yellow
IPA
MDC
Colour Erythrosine

Secnidazole:
Starch
Microcrystaline cellulose powder
Gelatine
Povidone K 30
Sodium Benzoate
Magnesium Stearate
Purified talc
Colloidal silicon dioxide
Cross Carmellose Sodium
Film Coating
HPMC
Talcum
Propylene Glycol
Titanium dioxide
Tartrazine Yellow
IPA
MDC
Colour Erythrosine

6.2 Incompatibilities
Not Applicable

6.3 Shelf-Life
Azithromycin: 36 months
Fluconazole: 36 Months
Secnidazole: 36 Months

6.4 Special Precautions for storage
Store below 30°C in a cool & dry place.

6.5 Nature and Content of container
Blister pack of 4 tablets in an inner carton with package insert
One tablet of Azithromycin, one tablet of fluconazole and 2 tablets of secnidazole.

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder
National Pharmacy Ltd,
P.O.Box 17843-00500,
Nairobi

Manufacturer:

Zain Pharma limited

Plot No: 209/13741, Colchester Park,

Go-Down No.1, 2, 3, Off Mombasa Road, Behind Nice And Lovely House, P.O. Box: 100167-00101, Nairobi, Kenya

8. Marketing Authorization Number
CTD 9408

9. Date of first authorization/renewal of the authorization
03/03/2023

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

11. Dosimetry
Not Applicable

12. Instructions for preparation of Radiopharmaceuticals
Not Applicable