Summary of Product Characteristics

(Product Data Sheet)

1. Name of the Finished Pharmaceutical Product

1.1 Product Name: DAZEL KIT

(Azithromycin Tablets 1g, Secnidazole Tablets 1 g and Fluconazole Tablets 150mg)

1.2 Strength: Each Kit contains

(a) Azithromycin Tablets 1 g (1 Tablet)
Each film coated tablet contains:
Azithromycin Dihydrate USP
equivalent to Anhydrous Azithromycin…….. 1 g
Colour: Titanium Dioxide

(b) Secnidazole Tablets 1 g (2 Tablets)
Each film coated tablet contains:
Secnidazole……... 1 g
Colour: Titanium Dioxide and Yellow Oxide of Iron

(c) Fluconazole Tablets 150 mg (1 Tablet)
Each uncoated tablet contains:
Fluconazole…… 150 mg
Colour: Ponceau 4R

1.3 Pharmaceutical Dosage Form: Tablets

2. Quality and Quantitative Composition

2.2 Quantitative Declaration:

Sr. No.	Ingredients	Theoretical quantity per tablet in mg
A) Fluconazole Tablets 150mg		
1.	Fluconazole USP	150.000
2.	Maize Starch BP	46.150
3.	Microcrystalline Cellulose BP	40.000
4.	Croscarmellose Sodium USP/NF	10.000
5.	Colour Ponceau 4R Lake IH	0.350
6.	Purified Water#$	q.s.
7.	Colloidal Silicon Dioxide USP/NF	1.000
8.	Magnesium Stearate BP	2.500
Total Weight of Tablet		***250.000mg***
B) Azithromycin Tablets 1 g		
1.	Azithromycin Dihydrate USP	1048.000
2.	Dibasic Calcium Phosphate Dihydrate BP	67.000
3.	Maize Starch BP	42.600
4.	Croscarmellose Sodium USP/NF	41.000
5.	Sodium Lauryl Sulphate BP	13.000
6.	Povidone (P.V.P.K-30) USP	39.000

Sr. No.	Ingredients	Theoretical quantity per tablet in mg
7.	Purified Water#$	q.s.
8.	Crospovidone BP	13.000
9.	Colloidal Silicon Dioxide USP/NF	10.400
10.	Purified Talc BP	13.000
11.	Magnesium Stearate BP	13.000
12.	Instacoat Sol (IC-S-223) White IH	39.000
13.	Isopropyl Alcohol BP $	q.s.
14.	Methylene Chloride BP $	q.s.
Total Weight of Tablet		***1339.000mg***
C) Secnidazole Tablets 1 g		
1.	Secnidazole IH	1000.000
2.	Microcrystalline Cellulose BP	72.000
3.	Povidone (PVPK-30) USP	40.000
4.	Purified Water#$	q.s.
5.	Sodium Starch Glycolate BP	25.000
6.	Colloidal Silicon Dioxide USP/NF	12.000
7.	Croscarmellose Sodium USP/NF	65.000
8.	Magnesium Stearate BP	6.000
9.	Wincoat WT 1540 Yellow IH	36.600
10.	Isopropyl Alcohol BP$	q.s.
11.	Methylene Chloride BP$	q.s.
Total Weight of Tablet		***1256.600mg***

$ Not present in final product.

Instacoat Sol IC-S-223 White comprises of Hydroxypropyl Methyl Cellulose, Polyethylene Glycol, Talcum Powder and Titanium Dioxide.

Wincoat WT 1540 Yellow comprises of Hydroxypropyl Methyl Cellulose, Diethyl Phthalate, Talcum Powder, Titanium Dioxide and Yellow Iron Oxide.

Purified water conforms to the specifications of IP/BP/USP/Ph.Eur./IH.

BP : British Pharmacopoeia
USP : United States Pharmacopoeia
USP/NF : United States Pharmacopoeia National Formulary
IH : In-House Specification
Ph. Eur. : European Pharmacopoeia
IP : Indian Phrmacopeia

3. Pharmaceutical Form:

Azithromycin Tablets 1g: White coloured, capsule shaped, film coated tablets.
Secnidazole Tablets 1g: Yellow coloured, capsule shaped, film coated tablets with breakline on one side.
Fluconazole Tablets 150mg: Pink coloured, slightly mottled appearance, round, flat uncoated tablets with breakline on one side.

4. Clinical Particulars

4.1 Therapeutic Indications :

The combination kit with azithromycin, secnidazole and fluconazole is more effective with better symptomatic relief and less recurrence rate and may be routinely recommended in all cases of lower genital infections and syndromic management of pelvic inflammatory disease in a safe and effective strategy.

The combination kit is indicated for

- Trichomoniasis
- Bacterial vaginosis
- Vaginal discharge due to Candidiasis
- Infections or mixed infections with Chlamydia and Neisseria

4.2 Posology and Method of administration :

For oral use only

This combination kit is meant for single dose therapy with the individual components to be administered concomitantly.

Azithromycin 1 g Tablets as a single oral dose to be administered with or without food

Secnidazole 2 g single dose. (administration of 2 Tablets)

Fluconazole 150 mg orally as a single dose with or without food.

Method of administration

The tablets to be swallowed as whole.

4.3 Contraindications :

Dazel Kit contains three chemotherapeutic agents:

Azithromycin, Secnidazole and Fluconazole. These 3 drugs do not cause drugs interactions when given together on the same day concomitantly.

Azithromycin

Contraindicated in patients

- With known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide drug.
- With a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin.

Secnidazole

- Hypersensitivity to imidazole derivatives.
- Pregnant and breastfeeding women

Fluconazole

- Contraindicated in patients who have shown hypersensitivity to fluconazole or to any

of its excipients. There is no information regarding cross-hypersensitivity between fluconazole and other azole antifungal agents. Caution should be used in prescribing fluconazole to patients with hypersensitivity to other azoles.

- Co-administration of terfenadine is contraindicated in patients receiving fluconazole at multiple doses of 400 mg or higher based upon results of a multiple dose interaction study.
- Co administration of other drugs known to prolong the QT interval and which are metabolized via the enzyme CYP3A4 such as cisapride, astemizole, erythromycin, pimozide, and quinidine are contraindicated in patients receiving fluconazole.

4.4 Special warning and precautions for use:

Azithromycin

Hypersensitivity

Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported in patients on azithromycin therapy.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that allergic symptoms may reappear when symptomatic therapy has been discontinued.

Hepatotoxicity

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.

QT Prolongation

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen with treatment with macrolides, including azithromycin. Cases of torsades de pointes have been spontaneously reported during post-marketing surveillance in patients receiving azithromycin. Providers should consider the risk of QT prolongation which can be fatal when weighing the risks and benefits of azithromycin for at-risk groups including:

- patients with known prolongation of the QT interval, a history of torsades de pointes, congenital long QT syndrome, bradyarrhythmias or uncompensated heart failure
- patients on drugs known to prolong the QT interval
- patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents.

Elderly patients may be more susceptible to drug-associated effects on the QT interval.

Clostridium difficile-Associated Diarrhea (CDAD)

Clostridium difficile-associated diarrhea 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.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

Exacerbation of Myasthenia Gravis

Exacerbation of symptoms of myasthenia gravis and new onset of myasthenic syndrome have been reported in patients receiving azithromycin therapy.

Use in Sexually Transmitted Infections

Azithromycin, at the recommended dose, should not be relied upon to treat syphilis. Antibacterial agents used to treat non-gonococcal urethritis may mask or delay the symptoms of incubating syphilis. All patients with sexually transmitted urethritis or cervicitis should have a serologic test for syphilis and appropriate testing for gonorrhea performed at the time of diagnosis. Appropriate antibacterial therapy and follow-up tests for these diseases should be initiated if infection is confirmed.

Development of Drug-Resistant Bacteria

Prescribing Azithromycin in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Secnidazole

- Alcoholic drinks should be avoided during secnidazole treatment.
- Do not administer to subjects with a history of blood dyscrasia

Fluconazole

Tinea capitis

Fluconazole has been studied for treatment of tinea capitis in children. It was shown not to be superior to griseofulvin and the overall success rate was less than 20%. Therefore, Diflucan should not be used for tinea capitis.

Cryptococcosis

The evidence for efficacy of fluconazole in the treatment of cryptococcosis of other sites (e.g. pulmonary and cutaneous cryptococcosis) is limited, which prevents dosing recommendations.

Deep endemic mycoses

The evidence for efficacy of fluconazole in the treatment of other forms of endemic mycoses such as paracoccidioidomycosis, lymphocutaneous sporotrichosis and histoplasmosis is limited, which prevents specific dosing recommendations.

Renal system

Fluconazole should be administered with caution to patients with renal dysfunction.

Hepatobiliary system

Fluconazole should be administered with caution to patients with liver dysfunction.

Fluconazole has been associated with rare cases of serious hepatic toxicity including fatalities, primarily in patients with serious underlying medical conditions. In cases of fluconazole associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of patient has been observed. Fluconazole hepatotoxicity has usually been reversible on discontinuation of therapy.

Patients who develop abnormal liver function tests during fluconazole therapy must be monitored closely for the development of more serious hepatic injury.

The patient should be informed of suggestive symptoms of serious hepatic effect (important asthenia, anorexia, persistent nausea, vomiting and jaundice). Treatment of fluconazole should be immediately discontinued and the patient should consult a physician.

Cardiovascular system

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. Fluconazole causes QT prolongation via the inhibition of Rectifier Potassium Channel current (Ikr). The QT prolongation caused by other medicinal products (such as amiodarone) may be amplified via the inhibition of cytochrome P450 (CYP) 3A4. Patients with hypokalemia and advanced cardiac failure are at an increased risk for the occurrence of life threatening ventricular arrhythmias and torsades de pointes.

Fluconazole should be administered with caution to patients with these potentially proarrhythmic conditions. Co-administration of other medicinal products known to prolong the QT interval and which are metabolized via the cytochrome P450 (CYP) 3A4 are contraindicated.

Halofantrine

Halofantrine has been shown to prolong QTc interval at the recommended therapeutic dose and is a substrate of CYP3A4. The concomitant use of fluconazole and halofantrine is therefore not recommended.

Dermatological reactions

Patients have rarely 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 severe cutaneous reactions to many medicinal

products. If a rash, which is considered attributable to fluconazole, develops in a patient treated for a superficial fungal infection, further therapy with this medicinal product 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.

Hypersensitivity
In rare cases anaphylaxis has been reported.

Cytochrome P450
Fluconazole is a moderate CYP2C9 and CYP3A4 inhibitor. Fluconazole is also an inhibitor of CYP2C19. Fluconazole treated patients who are concomitantly treated with medicinal products with a narrow therapeutic window metabolized through CYP2C9, CYP2C19 and CYP3A4, should be monitored.

Terfenadine
The co-administration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.

4.5 Interactions with other medicinal products and other forms of Interactions :
Azithromycin
Nelfinavir
Co-administration of nelfinavir at steady-state with a single oral dose of azithromycin resulted in increased azithromycin serum concentrations. Although a dose adjustment of azithromycin is not recommended when administered in combination with nelfinavir, close monitoring for known adverse reactions of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted.

Warfarin
Spontaneous post-marketing reports suggest that concomitant administration of azithromycin may potentiate the effects of oral anticoagulants such as warfarin, although the prothrombin time was not affected in the dedicated drug interaction study with azithromycin and warfarin. Prothrombin times should be carefully monitored while patients are receiving azithromycin and oral anticoagulants concomitantly.

Potential Drug-Drug Interactions with Macrolides
Interactions with digoxin or phenytoin have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interactions. However, drug interactions have been observed with other macrolide products. Until further data are developed regarding drug interactions when digoxin or phenytoin are used concomitantly with azithromycin careful monitoring of patients is advised.

Secnidazole

Contraindicated combination therapy:

- Disulfiram: Delirious episodes, confusion.
- Alcohol: Hotness, redness, vomiting, tachycardia. Avoid alcoholic drinks and alcohol-containing medicine.

Combinations subject to precautions:

- Oral anticoagulants (warfarin): Potentiation of the oral anticoagulant and increased risk of hemorrhage by lowering of its hepatic catabolism.

More frequent determination of the prothrombin time and monitoring of the INR. Adjustment of the oral anticoagulant dose during secnidazole treatment and 8 days after its withdrawal.

Fluconazole

Concomitant use of the following other medicinal products is contraindicated:

Cisapride: There have been reports of cardiac events including torsades de pointes in patients to whom fluconazole and cisapride were co-administered.
Concomitant treatment with fluconazole and cisapride is contraindicated.

Terfenadine: Because of the occurrence of serious cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receiving azole antifungals in conjunction with terfenadine, interaction studies have been performed.
The combined use of fluconazole at doses of 400 mg or greater with terfenadine is contraindicated. The co-administration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.

Astemizole: Concomitant administration of fluconazole with astemizole may decrease the clearance of astemizole.
Resulting increased plasma concentrations of astemizole can lead to QT prolongation and rare occurrences of torsades de pointes. Co-administration of fluconazole and astemizole is contraindicated.

Pimozide: Although not studied in vitro or in vivo, concomitant administration of fluconazole with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can lead to QT prolongation and rare occurrences of torsades de pointes. Co-administration of fluconazole and pimozide is contraindicated.

Quinidine: Although not studied in vitro or in vivo, concomitant administration of fluconazole with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with QT prolongation and rare occurrences of
torsades de pointes. Co-administration of fluconazole and quinidine is contraindicated.

Erythromycin: Concomitant use of fluconazole and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, torsades de pointes) and consequently sudden heart death. Co-administration of fluconazole and erythromycin is contraindicated.

Concomitant use that should be used with caution

Amiodarone: concomitant administration of fluconazole with amiodarone may increase QT prolongation. Therefore, caution should be taken when both drugs are combined, notably with high dose fluconazole (800 mg).

Concomitant use of the following other medicinal products lead to precautions and dose adjustments:

The effect of other medicinal products on fluconazole

Hydrochlorothiazide: In a pharmacokinetic interaction study, co-administration of multiple-dose hydrochlorothiazide to healthy volunteers receiving fluconazole increased plasma concentration of fluconazole by 40%. An effect of this magnitude should not necessitate a change in the fluconazole dose regimen in subjects receiving concomitant diuretics.

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.

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

The effect of fluconazole on other medicinal products

Fluconazole is a moderate inhibitor of cytochrome P450 (CYP) isoenzymes 2C9 and 3A4. Fluconazole is also a strong inhibitor of the isozyme CYP2C19. In addition to the observed/documented interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9, CYP2C19 and CYP3A4 coadministered with fluconazole. Therefore caution should be exercised when using these combinations and the patients should be carefully monitored. The enzyme inhibiting effect of fluconazole persists 4-5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole.

Alfentanil: During concomitant treatment with fluconazole (400 mg) and intravenous alfentanil (20 µg/kg) in healthy volunteers the alfentanil AUC_{10} increased 2-fold, probably through inhibition of CYP3A4. Dose adjustment of alfentanil may be necessary.

Amitriptyline, nortriptyline: Fluconazole increases the effect of amitriptyline and nortriptyline. 5-nortriptyline and/or S-amitriptyline may be measured at initiation of the combination therapy and after one week. Dose of amitriptyline/nortriptyline should be adjusted, if necessary

Amphotericin B: Concurrent administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small additive antifungal effect in systemic infection with *C. albicans*, no interaction in intracranial infection with *Cryptococcus neoformans*, and antagonism of the two medicinal products in systemic infection with *Aspergillus fumigatus*. The clinical significance of results obtained in these studies is unknown.

Anticoagulants: In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria, and melena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. During concomitant treatment with fluconazole and warfarin the prothrombin time was prolonged up to 2-fold, probably due to an inhibition of the warfarin metabolism through CYP2C9. In patients receiving coumarin-type anticoagulants or indanedione anticoagulants concurrently with fluconazole the prothrombin time should be carefully monitored. Dose adjustment of the anticoagulant may be necessary.

Benzodiazepines (short acting), i.e. midazolam, triazolam: Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dose, and the patients should be appropriately monitored.

Carbamazepine: Fluconazole inhibits the metabolism of carbamazepine and an increase in serum carbamazepine of 30% has been observed. There is a risk of developing carbamazepine toxicity. Dose adjustment of carbamazepine may be necessary depending on concentration measurements/effect.

Calcium channel blockers: Certain calcium channel antagonists (nifedipine, isradipine, amlodipine, verapamil and felodipine) are metabolized by CYP3A4. Fluconazole has the potential to increase the systemic exposure of the calcium channel antagonists. Frequent monitoring for adverse events is recommended.

Celecoxib: During concomitant treatment with fluconazole (200 mg daily) and celecoxib (200 mg) the celecoxib C_{max} and AUC increased by 68% and 134%, respectively. Half of the celecoxib dose may be necessary when combined with fluconazole.

Cyclophosphamide: Combination therapy with cyclophosphamide and fluconazole results in an increase in serum bilirubin and serum creatinine. The combination may be used while taking increased consideration to the risk of increased serum bilirubin and serum creatinine.
Fentanyl: In healthy volunteers that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression. Patients

should be monitored closely for the potential risk of respiratory depression. Dosage adjustment of fentanyl may be necessary.

HMG CoA reductase inhibitors: The risk of myopathy and rhabdomyolysis increases when fluconazole is co-administered with HMG-CoA reductase inhibitors metabolised through CYP3A4, such as atorvastatin and simvastatin, or through CYP2C9, such as fluvastatin. If concomitant therapy is necessary, the patient should be observed for symptoms of myopathy and rhabdomyolysis and creatinine kinase should be monitored. HMG-CoA reductase inhibitors should be discontinued if a marked increase in creatinine kinase is observed or myopathy/rhabdomyolysis is diagnosed or suspected.

Olaparib: Moderate inhibitors of CYP3A4 such as fluconazole increase olaparib plasma concentrations; concomitant use is not recommended. If the combination cannot be avoided, limit the dose of olaparib to 200 mg twice daily.

Immunosuppresors (i.e. cyclosporine, everolimus, sirolimus and tacrolimus)
Cyclosporine: Fluconazole significantly increases the concentration and AUC of cyclosporine.This combination may be used by reducing the dose of cyclosporine depending on cyclosporine concentration.

Everolimus: Although not studied *in vivo* or *in vitro*, fluconazole may increase serum concentrations of everolimus through inhibition of CYP3A4.

Sirolimus: Fluconazole increases plasma concentrations of sirolimus presumably by inhibiting the metabolism of sirolimus via CYP3A4 and P-glycoprotein. This combination may be used with a dose adjustment of sirolimus depending on the effect/concentration measurements.

Tacrolimus: Fluconazole may increase the serum concentrations of orally administered tacrolimus up to 5 times due to inhibition of tacrolimus metabolism through CYP3A4 in the intestines. Increased tacrolimus levels have been associated with nephrotoxicity. Dose of orally administered tacrolimus should be decreased depending on tacrolimus concentration.

Losartan: Fluconazole inhibits the metabolism of losartan to its active metabolite (E-31 74) which is responsible for most of the angiotensin Il-receptor antagonism which occurs during treatment with losartan. Patients should have their blood pressure monitored continuously.

Methadone: Fluconazole may enhance the serum concentration of methadone. Dose adjustment of methadone may be necessary.

Non-steroidal anti-inflammatory drugs: Fluconazole has the potential to increase the systemic exposure of other NSAIDs that are metabolized by CYP2C9 (e.g. naproxen,

lornoxicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dose of NSAIDs may be needed.

Phenytoin: Fluconazole inhibits the hepatic metabolism of phenytoin. With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.

Prednisone: Patients on long-term treatment with fluconazole and prednisone should be carefully monitored for adrenal cortex insufficiency when fluconazole is discontinued.

Rifabutin: Fluconazole increases serum concentrations of rifabutin, leading to increase in the AUC of rifabutin up to 80%. There have been reports of uveitis in patients to whom fluconazole and rifabutin were coadministered. In combination therapy, symptoms of rifabutin toxicity should be taken into consideration.

Saquinavir: Fluconazole increases the AUC and C_{max} of saquinavir with approximately 50% and 55% respectively, due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Interaction with saquinavir/ritonavir has not been studied and might be more marked. Dose adjustment of saquinavir may be necessary.

Sulfonylureas: Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulfonylureas (e.g., chlorpropamide, glibenclamide, glipizide, tolbutamide) in healthy volunteers. Frequent monitoring of blood glucose and appropriate reduction of sulfonylurea dose is recommended during coadministration.

Theophylline: Patients who are receiving high dose theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole. Therapy should be modified if signs of toxicity develop.

Vinca alkaloids: Although not studied, fluconazole may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity, which is possibly due to an inhibitory effect on CYP3A4.

Vitamin A: This combination may be used but the incidence of CNS related undesirable effects should be borne in mind.

Voriconazole: (CYP2C9 and CYP3A4 inhibitor): Monitoring for voriconazole associated adverse events is recommended if voriconazole is used sequentially after fluconazole.

Zidovudine: Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions. Dose reduction of zidovudine may be considered.

Ivacaftor: Coadministration with ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, increased ivacaftor exposure by 3fold and hydroxymethyl-ivacaftor (M1) exposure by 1.9fold. A reduction of the ivacaftor dose to 150 mg once daily is recommended for patients taking concomitant moderate CYP3A inhibitors, such as fluconazole and erythromycin.

4.6 Pregnancy and Lactation :

Pregnancy

Azithromycin

Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose concentrations (i.e., 200 mg/kg/day). These daily doses in rats and mice, based on body surface area, are estimated to be 4 and 2 times, respectively, an adult daily dose of 500 mg. In the animal studies, no evidence of harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

Secnidazole

No teratogenic effects are observed during animal experimentation. However, in view of the absence of data in humans, it is not recommended to take secnidazole during pregnancy.

Fluconazole

Teratogenic Effects:

Pregnancy Category C

There are no adequate and well-controlled studies of fluconazole in pregnant women. Available human data do not suggest an increased risk of congenital anomalies following a single maternal dose of 150 mg

Lactation

Azithromycin

Azithromycin has been reported to be excreted in human breast milk in small amounts.

Secnidazole

Secnidazole is excreted in breast milk.

Fluconazole

Fluconazole is secreted in human milk at concentrations similar to maternal plasma concentrations.

Therefore Dazel Kit is not recommended in nursing mother.

4.7 Effects on ability to drive and use machine :

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

Rare cases of dizziness have been reported with imidazole derivatives.
No studies have been performed on the effects of Fluconazole on the ability to drive or use machines.

Patients should be warned about the potential for dizziness while taking individual components of Dazel Kit and should be advised not to drive or operate machines if any of these symptoms occur.

4.8 Undesirable Effects :

Dazel Kit is well tolerated with a low incidence of side effects. Most common advesrse events of individual drugs are given below;

Azithromycin

Overall, the most common adverse reactions in patients receiving azithromycin were related to the gastrointestinal system included diarrhea/loose stools (7%), nausea (5%), abdominal pain (5%), vomiting (2%), and dyspepsia (1%).

Secnidazole

The following undesirable effects seen with imidazole derivatives may occur:

- Most frequently: digestives disorders, with abdominal pain, change in taste (metallic), glossitis, and stomatitis.
- Urticaria.
- Moderate leucopenia, reversible upon withdrawal of treatment.
- Rarely dizziness, lack of coordination and ataxia, paresthesia, sensitive and motor polyneuritis.
- Rare cases of digestive disorders have been reported (nausea, vomiting, gastric pain).

Fluconazole

Fluconazole is generally well tolerated.

In Patients Receiving a Single Dose for Vaginal Candidiasis

The most common treatment-related adverse events reported in the patients who received 150 mg single dose fluconazole for vaginitis were headache (13%), nausea (7%), and abdominal pain (6%). Other side effects reported with an incidence equal to or greater than 1% included diarrhea (3%), dyspepsia (1%), dizziness (1%), and taste perversion (1%). Most of the reported side effects were mild to moderate in severity. Rarely, angioedema and anaphylactic reaction have been reported in marketing experience.

In Patients Receiving Multiple Doses for Other Infections

The following treatment-related clinical adverse events occurred at an incidence of 1% or greater in patients receiving Fluconazole for 7 or more days in clinical trials: nausea 3.7%, headache 1.9%, skin rash 1.8%, vomiting 1.7%, abdominal pain 1.7%, and diarrhea 1.5%.

Post-Marketing Experience

In addition, the following adverse events have occurred during post-marketing experience.

Immunologic: In rare cases, anaphylaxis (including angioedema, face edema and pruritus) has been reported.

Body as a Whole: Asthenia, fatigue, fever, malaise.

Cardiovascular: QT prolongation, torsade de pointes.

Central Nervous System: Seizures, dizziness.

Hematopoietic and Lymphatic: Leukopenia, including neutropenia and agranulocytosis, thrombocytopenia.

Metabolic: Hypercholesterolemia, hypertriglyceridemia, hypokalemia.

Gastrointestinal: Cholestasis, dry mouth, hepatocellular damage, dyspepsia, vomiting.

Other Senses: Taste perversion.

Musculoskeletal System: myalgia.

Nervous System: Insomnia, paresthesia, somnolence, tremor, vertigo.

Skin and Appendages: Acute generalized exanthematous-pustulosis, drug eruption, increased sweating, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis, alopecia.

4.9 Overdosage:

Azithromycin

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

Fluconazole

There have been reports of overdose with fluconazole accompanied by hallucination and paranoid behavior.

In the event of overdose, symptomatic treatment (with supportive measures and gastric lavage if clinically indicated) should be instituted.

Fluconazole is largely excreted in urine. A three-hour hemodialysis session decreases plasma levels by approximately 50%.

In mice and rats receiving very high doses of fluconazole, clinical effects in both species included decreased motility and respiration, ptosis, lacrimation, salivation, urinary incontinence, loss of righting reflex, and cyanosis; death was sometimes preceded by clonic convulsions.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties:

Azithromycin

Azithromycin is a macrolide antibiotic belonging to the azalide group. The molecule is constructed by adding a nitrogen atom to the lactone ring of erythromycin A. The chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin A. The molecular weight is 749.0. The mechanism of action of azithromycin is based upon the suppression of bacterial protein synthesis by means of binding to the ribosomal 50S sub-unit and inhibition of peptide translocation.

Antibacterial spectrum of Azithromycin

Commonly susceptible species
Aerobic Gram-positive microorganisms
Staphylococcus aureus
Methycillin-susceptible
Streptococcus pneumoniae
Penicillin-susceptible
Streptococcus pyogenes (Group A)

Aerobic Gram-negative microorganisms
Haemophilus influenzae
Haemophilus parainfluenzae
Legionella pneumophila
Moraxella catarrhalis
Neisseria gonorrhoeae
Pasteurella multocida

Anaerobic microorganisms
Clostridium perfringens
Fusobacterium spp.
Prevotella spp.
Porphyromonas spp.

Other microorganisms
Chlamydia trachomatis

Secnidazole

Secnidazole is a nitroimidazole antimicrobial drug that displays selectivity against many anaerobic Gram-positive and Gram-negative bacteria and protozoa. In vitro studies demonstrates the effectiveness of the drug against *Bacteroides fragilis, Trichomonas vaginalis, Entamoeba histolytica and Giardia lamblia*. There is no significant bacterial or protozoal resistance reported from secnidazole treatment.

Secnidazole enters the bacterial cell as a prodrug without an antimicrobial activity. The drug is converted to an active form via reduction of nitro groups to radical anions by bacterial enzymes. The radical anions are thought to interfere with bacterial DNA synthesis of susceptible isolates

Fluconazole

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 antifungal activity 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.

Susceptibility in vitro:

In vitro, fluconazole displays antifungal activity against most clinically common *Candida species (including C. albicans, C. parapsilosis, C. tropicalis). C. glabrata* shows a wide range of susceptibility while *C. krusei* is resistant to fluconazole.

Fluconazole also exhibits activity in vitro against *Cryptococcus neoformans* and *Cryptococcus. gattii* as well as the endemic moulds *Blastomyces dermatiditis, Coccidioides immitis, Histoplasma capsulatum* and *Paracoccidioides brasiliensis*.

5.2 Pharmacokinetics Properties :

Azithromycin

Absorption

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

Distribution

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

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

Elimination

The terminal plasma elimination half-life closely reflects the elimination half-life from tissues of 24 days.

Secnidazole

Secnidazole is rapidly absorbed following oral administration. The maximum serum level is obtained after 3 hours following oral administration of 2 gm secnidazole.

The plasma elimination half-life is about 20 hours. The majority of secnidazole is eliminated via urine (50% of the ingested dose is excreted within 120 hours).

The pharmacokinetic profile of secnidazole gives it the longest half-life of all the second generation nitroimidazoles, ensuring 72-hour therapeutic blood levels from a 2 gm single dose.

Fluconazole

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous 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 absorption is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0.5 and 1.5 hours post-dose. Plasma concentrations are proportional to dose. Ninety percent steady state levels are reached by day 4-5 with multiple once daily dosing. Administration of a loading dose (on day 1) of twice the usual daily dose enables plasma levels to approximate to 90% steady-state levels by day 2.

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% the corresponding plasma levels.

High skin concentration of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. At a dose of 50 mg once daily, the concentration of fluconazole after 12 days was 73 µg/g and 7 days after cessation of treatment the concentration was still 5.8 µg/g. At the 150 mg once-a-week dose, the concentration of fluconazole in stratum corneum on day 7 was 23.4 µg/g and 7 days after the second dose was still 7.1 µg/g.

Concentration of fluconazole in nails after 4 months of 150 mg once-a-week dosing was 4.05 µg/g in healthy and 1.8 µg/g in diseased nails; and, fluconazole was still measurable in nail samples 6 months after the end of therapy.

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 moderate inhibitor of the isozymes CYP2C9 and CYP3A4 (see section 4.5). Fluconazole is also a strong 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 medicinal product. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites.
The long plasma elimination half-life provides the basis for single dose therapy for vaginal candidiasis, once daily and once weekly dosing for other indications.

5.3 Preclinical Safety data :
Azithromycin
Phospholipidosis (intracellular phospholipid accumulation) has been observed in several tissues (e.g. eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and/or pancreas) of mice, rats, and dogs given multiple doses of azithromycin. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs. The effect has been shown to be reversible after cessation of azithromycin treatment. The significance of the finding for animals and humans is unknown.

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

Mutagenic potential:
There was no evidence of a potential for genetic and chromosome mutations in *in vivo* and *in vitro* test models.

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

Fluconazole
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the human exposure indicating little relevance to clinical use.

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 10 mg/kg/day had an increased incidence of

hepatocellular adenomas.

Mutagenesis

Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of Salmonella typhimurium, and in the mouse lymphoma L5178Y system. Cytogenetic studies in vivo (murine bone marrow cells, following oral administration of fluconazole) and in vitro (human lymphocytes exposed to fluconazole at 1000 µg/ml) showed no evidence of chromosomal mutations.

Reproductive toxicity

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10, or 20 mg/kg or with parenteral doses of 5, 25, or 75 mg/kg.

There were no foetal effects at 5 or 10 mg/kg; increases in foetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg to 320 mg/kg embryolethality in rats was increased and foetal abnormalities included wavy ribs, cleft palate, and abnormal cranio-facial ossification.

The onset of parturition was slightly delayed at 20 mg/kg orally and dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg and 40 mg/kg intravenously. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. These effects on parturition are consistent with the species specific oestrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole.

Secnidazole

Not Specified

6. Pharmaceutical Particulars

6.1 List of Excipients:

A) Fluconazole Tablet 150 mg

1. Maize Starch BP
2. Microcrystalline Cellulose BP
3. Croscarmellose Sodium USP/NF
4. Colour Ponceau 4R Lake IH
5. Colloidal silicon dioxide USP/NF
6. Magnesium stearate BP

B) Azithromycin Tablets 1 g

1. Dibasic Calcium Phosphate Dihydrate BP
2. Maize Starch BP
3. Croscarmellose Sodium USP/NF
4. Sodium Lauryl Sulphate BP

5. Povidone (P.V.P.K-30) USP
6. Crospovidone BP
7. Colloidal Silicon Dioxide USP/NF
8. Purified Talc BP
9. Magnesium Stearate BP
10. Instacoat Sol (IC-S-223) White IH
11. Isopropyl Alcohol BP
12. Methylene Chloride BP

c) Secnidazole Tablets 1 g

1. Microcrystalline Cellulose BP
2. Povidone (PVPK-30) USP
3. Sodium Starch Glycolate BP
4. Colloidal Silicon Dioxide USP/NF
5. Magnesium Stearate BP
6. Croscarmellose Sodium USP/NF
7. Wincoat WT 1540 Yellow IH
8. Isopropyl Alcohol BP
9. Methylene Chloride BP

6.2 Incompatibilities : Not Applicable

6.3 Shelf Life: 36 months

6.4 Special Precautions for storage: Store below 30^0C. Protect from light and moisture.

6.5 Nature and contents of container: Kit contains

Available as 4 tablets in clear Alu/PVC-PvdC blister pack, each blister packed in a printed carton along with pack insert.

7. Marketing Authorization Holder:

Ajanta Pharma Limited
Ajanta House,
Charkop, Kandivli (West),
Mumbai- 400 067,
India

8. Marketing Authorization Numbers: 6748/06/09

9. Date of first authorization/ renewal of the authorization: None

10. Date of revision of text: Apr, 2019.