MODULE 1 – ADMINISTRATIVE PARTICULARS OF THE PRODUCT

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1.3.1.1. Name of the medicinal product:

Cotozal TZ Plus

1.3.1.1.1 (Invented) name of the medicinal product:

Generic Name/INN Name: Combipack of Fluconazole Capsules BP, Tinidazole Tablets and Azithromycin Tablets USP

1.3.1.1.2 Strength:

Each Combipack Contains:
A. Fluconazole Capsules BP (1 Capsule)
Each hard gelatin capsule contains:
Fluconazole USP 150 mg
Excipients q.s.
Approved colours are used in empty hard gelatin capsule shell.
B. Tinidazole Tablets (2 Tablets)
Each film coated tablet contains:
Tinidazole BP 1gm
Excipients q.s.
Colour: Blue oxide of Iron
C. Azithromycin Tablets USP 1 gm (1 Tablet)
Each film coated tablet contains:
Azithromycin Dihydrate USP
Eq. to Azithromycin (anhydrous) 1 gm
Excipients q.s.
Colour: yellow oxide of Iron

1.3.1.1.3 Pharmaceutical form:

Fluconazole Capsules BP 150 mg - Capsule (Solid oral dosage form)

Tinidazole Tablets 1 gm - Tablet (Solid oral dosage form)

Azithromycin Tablets USP 1 gm - Tablet (Solid oral dosage form)

1.3.1.2. Qualitative and Quantitative composition: [Fluconazole Capsules BP 150 mg]

Sr. No.	Ingredients	Spec.	Label claim (mg)	Std. Qty./Cap (mg)	% w/w	Function
Dry Mixing						
1.	Fluconazole*	USP	150.000	150.000	48.387	Active
2.	Microcrystalline Cellulose Grade 102 **	BP	---	53.000	17.097	Diluent/ Disintegrant

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3.	Sodium Lauryl Sulphate	BP	---	7.000	2.258	Surfactant
4.	Magnesium Stearate	BP	---	5.000	1.613	Lubricant
5.	Colloidal Anhydrous Silica	BP	---	5.000	1.613	Glidant
6.	Lactose Monohydrate Granulated DCL-15 DC2050	BP	---	45.000	14.516	Diluent
7.	Lactose Monohydrate	BP	---	44.9903	14.513	Diluent
Total net content				**310.000**	**100.00**	
8.	EHG CAPS "2" Black /Red	In-House	---	01 Capsule = 63 mg	-	Capsule shell
Total weight of filled capsule with shell				**373.000**	-	

Note: * The quantity of the Fluconazole has to be calculated as per the Assay and LOD.
** Quantity of Microcrystalline Cellulose Grade 102 will vary as per the quantity of the APIs.

1.3.1.2. Qualitative and Quantitative composition: [Tinidazole Tablets 1 gm]

Sr. No.	Ingredients	Specification	Label Claim (mg)	Std. Qty. /Tablet (mg)	%w/w	Function
Dry Mixing						
1.	Tinidazole*	BP	1000.000	1000.000	71.685	Active
2.	Maize Starch**	BP	---	254.000	18.208	Diluent
3.	Crospovidone	BP	---	10.000	0.717	Super Disintegrant agent
Binding						
4.	PVPK 30 (Polyvinyl Pyrrolidone K-30)	BP	---	36.000	2.581	Binder
5.	Purified Water ***	BP	---	123.600	---	Solvent
Lubrication						
6.	Magnesium Stearate	BP	---	10.000	0.717	Lubricant
7.	Purified Talc	BP	---	14.000	1.004	Glidant
8.	Crospovidone	BP	---	20.000	1.434	Super Disintegrant agent
9.	Colloidal Anhydrous Silica	BP	---	6.000	0.430	Glidant
Total wt. of Uncoated Tablet				**1350.00**		
Coating						
10.	Denature Absolute Alcohol (DAA) with	In-House	---	0.315%	---	Solvent for coating

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	0.5 % Acetone ***					
11.	Dichloromethane***	BP	---	250.000	---	Solvent for coating
12.	Col. EZY 17F580022 (White)	In-House	---	40.000	2.867	Coating material
13.	Titanium Dioxide	BP	---	3.000	0.215	Opacifier
14.	Col.Brilliant Blue Lake	In-House	---	2.000	0.143	Colour
Total wt. of Film coated Tablet				**1395.00**	**100%**	

Note: * The quantity of the Tinidazole has to be calculated as per the Assay & LOD.

** Quantity of Maize Starch will vary as per the quantity of the APIs.

*** Used in film coating suspension preparation and it is evaporated on drying.

1.3.1.2. Qualitative and Quantitative composition: [Azithromycin Tablets USP 1 gm]

Sr. No.	Ingredients	Specifications	Label Claim (mg)	Qty./ Tablet (mg)	% w/w	Function
1.	Azithromycin * eq to Anhydrous Azithromycin	USP	1000.000	1000.000	75.086	Active
2.	Micro crystalline Cellulose Powder**	BP	---	147.410	6.580	Diluent
3.	Croscarmellose Sodium	BP	---	20.000	1.423	Superdisinte-grant
4.	Sodium Lauryl Sulphate	BP	---	3.000	0.214	Surfactant
5.	Starch 1500	BP	---	40.000	2.847	Disintegrant/ Binder
6.	PVP K- 30 (Polyvinyl Pyrrolidone K-30)	BP	---	30.000	2.135	Binder
7.	Microcrystalline Cellulose Grade 102	BP	---	81.590	5.807	Diluent
8.	Colloidal Anhydrous Silica	BP	---	14.000	0.996	Glidant
9.	Croscarmellose Sodium	BP	---	20.000	1.423	Superdisinte-grant
10.	Magnesium Stearate	BP	---	14.000	0.996	Lubricant
Total wt. of uncoated Tablet				**1370.000 mg**		
Film Coating						
11.	Denature Absolute Alcohol (DAA) with	In-House	---	0.315 ml	---	Coating Solvent

	0.5 % Acetone ***					
12.	Dichloromethane***	BP	---	374.800	---	Coating Solvent
13.	Col.Elegance Coat EL-OY- 8005 Yellow (Iron Oxide of Yellow)	In-House	---	35.000	2.491	Coating material
Total wt. of Film coated Tablet				**1405.00 mg**	**100 %**	

Note:
* The quantity of the Azithromycin has to be calculated as per the Assay and Water content.
** Quantity of Microcrystalline Cellulose Powder will vary as per the quantity of the APIs.
*** Used in film coating suspension preparation and it is evaporated on drying.

1.3.1.3. Pharmaceutical form: [Fluconazole Capsules BP 1 gm]

Dosage Form: Solid oral dosage form- Capsule

Visual & Physical characteristics of the product:
A back/red coloured hard gelatin capsule size "2" containing white coloured crystalline powder.

1.3.1.4. Clinical particulars [Fluconazole Capsules BP 1 gm]

1.3.1.4.1. Therapeutic indications:
Treatment of Vaginal discharge or itching resulting from single or multiple infections due to vaginal candidiasis, bacterial vaginosis, trichomoniasis and non-complicated gonorrhea.

1.3.1.4.2. Posology and method of administration: [Fluconazole Capsules BP 1 gm]
The dose should be based on the nature and severity of the fungal infection. Treatment of infections requiring multiple dosing should be continued until clinical parameters or laboratory tests indicate that active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection.

Special populations
Elderly
Dosage should be adjusted based on the renal function (see “Renal impairment”).
Renal impairment
Fluconazole is predominantly excreted in the urine as unchanged active substance.
No adjustments in single dose therapy are necessary. In patients (including paediatric population) with impaired renalfunction who will receive multiple doses of fluconazole, an initial dose of 50 mg to 400 mg should be given, based on therecommended daily dose for the indication. After this initial loading dose, the daily dose (according to indication) shouldbe based on the following table:

Creatinine clearance (ml/min)	**Percent of recommended dose**
>50	100%
≤50 (no haemodialysis)	50%
Haemo dialysis	100% after each haemodialysis

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Patients on haemo dialysis should receive 100% of the recommended dose after each haemo dialysis; on non-dialysisdays, patients should receive a reduced dose according to their creatinine clearance.

Hepatic impairment

Limited data are available in patients with hepatic impairment, therefore fluconazole should be administered with caution to patients with liver dysfunction

Paediatric population

A maximum dose of 400 mg daily should not be exceeded in paediatric population.

As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. Fluconazole is administered as a single daily dose.

For paediatric patients with impaired renal function, see dosing in "Renal impairment". The pharmacokinetics of fluconazole has not been studied in paediatric population with renal insufficiency (for "Term newborn infants" who oftenexhibit primarily renal immaturity please see below).

Infants, toddlers and children (from 28 days to 11 years old):

Indication	Posology	Recommendations
Mucosal candidiasis	Initial dose: 6 mg/kg Subsequent dose: 3 mg/kg once daily	Initial dose may be used on the first day to achieve steady state levels more rapidly
Invasive candidiasis Cryptococcal meningitis	Dose: 6 to 12 mg/kg once daily	Depending on the severity of the disease
Maintenance therapy to preventrelapse of cryptococcal meningitisin children with high risk of recurrence	Dose: 6 mg/kg once daily	Depending on the severity of the disease
Prophylaxis of Candida inimmunocompromised patients	Dose: 3 to 12 mg/kg once daily	Depending on the extent and duration ofthe induced neutropenia (see Adultsposology)

Adolescents (from 12 to 17 years old):

Depending on the weight and pubertal development, the prescriber would need to assess which posology (adults or children) is the most appropriate. Clinical data indicate that children have a higher fluconazole clearance than observed for adults. A dose of 100, 200 and 400 mg in adults corresponds to a 3, 6 and 12 mg/kg dose in children to obtain a comparable systemic exposure.

Safety and efficacy for genital candidiasis indication in paediatric population has not been established. Current available safety data for other paediatric indications are described in section 4.8. If treatment for genital candidiasis is imperative in adolescents (from 12 to 17 years old), the posology should be the same as adult's posology.

Term newborn infants (0 to 27 days):

Neonates excrete fluconazole slowly. There are few pharmacokinetic data to support this posology in term new born infants.

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Age group	Posology	Recommendations
Term newborn infants (0 to 14 days)	The same mg/kg dose as for infants, toddlers and children should be given every 72 hours	A maximum dose of 12 mg/kg every 72hours should not be exceeded
Term newborn infants (from 15 to27 days)	The same mg/kg dose as for infants, toddlers and children should be given every 48 hours	A maximum dose of 12 mg/kg every 48hours should not be exceeded

Method of administration

Fluconazole may be administered either orally (Capsules and powder for oral suspension) or by intravenous infusion (Solution for infusion), the route being dependent on the clinical state of the patient. On transferring from the intravenous to the oral route, or vice versa, there is no need to change the daily dose.

The physician should prescribe the most appropriate pharmaceutical form and strength according to age, weight and dose. The capsule formulation is not adapted for use in infants and small children. Oral liquid formulations of fluconazole are available that are more suitable in this population the capsules should be swallowed whole and independent of food intake.

1.3.1.4.3. Contraindications: [Fluconazole Capsules BP 1 gm]

• Hypersensitivity to the active substance, to related azole substances, or to any of the excipients listed in section 6.1.

• Co-administration of terfenadine is contra-indicated in patients receiving fluconazole at multiple doses of 400 mg per day or higher based upon results of a multiple dose interaction study.

• Co-administration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 such as cisapride, astemizole, pimozide quinidine and erythromycin are contra-indicated in patients receiving fluconazole

1.3.1.4.4. Special warnings and precautions for use: [Fluconazole Capsules BP 1 gm]

WARNINGS:

Those who develop rashes due to fluconazole (in the Combikit) must be monitored closely. Fluconazole (in the Combikit) needs to be advocated with due precaution along with oral hypoglycemics, coumarins, phenytoin, cyclosporine, rifampicin, theophylline, astemizole, rifabutin, tacrolimus and short-acting benzodiazepines. As azithromycin interacts with aluminium and magnesium-containing antacids, digoxin, ergot derivatives, triazolam and drugs metabolized by cytochrome P450 such as carbamazepine, cyclosporine, phenytoin, the Combikit must be coadministered with care. Alcohol beverages must be avoided whilst taking the Combikit, and for three days thereafter since simultaneous intake of nitroimidazoles like tinidazole could result in abdominal cramps, flushing, nausea, vomiting, headaches and even psychotic reactions.

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PRECAUTIONS:

The Combikit is to be advocated with due precaution in hepatic and renal disease, and potentially proarrhythmic conditions in view potential of fluconazole and azithromycin to induce liver and kidney dysfunction, and cardiac conduction abnormalities. The Combikit should be advocated with care in diarrhea since azithromycin usage could be associated with pseudomembranous colitis.

1.3.1.4.5. Interaction with other medicinal products and other forms of interaction: [Fluconazole Capsules BP 1 gm]

Renal impairment:

Caution has to be taken.

Hepatic impairment:

Patients who develop abnormal liver function should be monitored.

Anticoagulants:

Fluconazole has been shown to prolong prothrombin time of coumarin drugs, hence requires careful monitoring. Cyclosporine: Concomitant administration of fluconazole and cyclosporine may result in increase in cyclosporine levels. Phenytoin: Fluconazole significantly increases phenytoin levels and A UC resulting in phenytoin toxicity.

Oral hypoglycaemics:

Concomitant administration of fluconazole and oral hypoglycaemics such as sulphonyl urea in diabetic patients results in increased plasma concentrations and reduced metabolism of antidiabetic agents.

Rifampicin:

Concomitant administration of fluconazole and rifampicin decreases A UC of fluconazole by 20%. Theophylline: Fluconazole may increase serum concentrations of theophylline.

Alcohol:

1.3.1.4.6. Pregnancy and lactation: [Fluconazole Capsules BP 1 gm]

PREGNANCY

An observational study has suggested an increased risk of spontaneous abortion in women treated with fluconazole during the first trimester.

There have been reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anteriorfontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers were treated for at least three or more months with high doses (400-800 mg daily) of fluconazole for coccidioidomycosis. The relationship between fluconazole use and these events is unclear.

Studies in animals have shown reproductive toxicity.

Data from several thousand pregnant women treated with a cumulative dose of ≤ 150 mg of fluconazole, administered in the first trimester, show no increase in the overall risk of malformations in the foetus. In one large observational cohort study, first trimester exposure to oral fluconazole was associated with a small increased risk of musculoskeletalmal formations, corresponding to approximately 1 additional case per 1000 women treated with cumulative doses ≤450mg compared with women treated with topical azoles and to approximately 4 additional cases per 1000 women treated with cumulative doses over 450

mg. The adjusted relative risk was 1.29 (95% CI 1.05 to 1.58) for 150 mg oral fluconazole and 1.98 (95% CI 1.23 to 3.17) for doses over 450 mg fluconazole.
Fluconazole in standard doses and short-term treatments should not be used in pregnancy unless clearly necessary.
Fluconazole in high dose and/or in prolonged regimens should not be used during pregnancy except for potentially life-threatening infections.

LACTATION
Fluconazole passes into breast milk to reach concentrations similar to those in plasma. Breast-feeding may be maintained after a single dose of 150 mg fluconazole. Breast-feeding is not recommended after repeated use or after high dose fluconazole. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for fluconazole and any potential adverse effects on the breast-fed child from fluconazole or from the underlying maternal condition.

1.3.1.4.7. Effects on ability to drive and use machines: [Fluconazole Capsules BP 1 gm]
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 or seizures while taking Fluconazole and should be advised not to drive or operate machines if any of these symptoms occur.

1.3.1.4.8. Undesirable effects: [Fluconazole Capsules BP 1 gm]
The most frequently (>1/10) reported adverse reactions are headache, abdominal pain, diarrhoea, nausea, vomiting, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased and rash. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with fluconazole treatment

Pediatric population:
The pattern and incidence of adverse reactions and laboratory abnormalities recorded during paediatric clinical trials, excluding the genital candidiasis indication, are comparable to those seen in adults.

1.3.1.4.9. Overdose: [Fluconazole Capsules BP 1 gm]
There have been reports of overdose with fluconazole, 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%.

1.3.1.5. Pharmacological properties: [Fluconazole Capsules BP 1 gm]

1.3.1.5.1. Pharmacodynamic properties:
Pharmacotherapeutic group: Antimycotics for systemic use, Triazole derivatives;
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 14alpha-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.

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.

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 reduced susceptibility to fluconazole while C. krusei and C. auris areresistant to fluconazole.

Fluconazole also exhibits activity in vitro against Cryptococcus neoformans and Cryptococcus. gattii as well as theendemic moulds Blastomyces dermatiditis, Coccidioides immitis, Histoplasma capsulatum and Paracoccidioidesbrasiliensis.

Pharmacokinetic/pharmacodynamic relationship

In animal studies, there is a correlation between MIC values and efficacy against experimental mycoses due to Candidaspp. In clinical studies, there is an almost 1:1 linear relationship between the AUC and the dose of fluconazole. There is also a direct though imperfect relationship between the AUC or dose and a successful clinical response of oral candidosis and to a lesser extent candidemia to treatment. Similarly cure is less likely for infections caused by strains with a higher fluconazole MIC.

Mechanisms of resistance

Candida spp have developed a number of resistance mechanisms to azole antifungal agents. Fungal strains which have developed one or more of these resistance mechanisms are known to exhibit high minimum inhibitory concentrations (MICs) to fluconazole which impacts adversely efficacy in vivo and clinically.

In usually susceptible species of Candida, the most commonly encountered mechanism of resistance develop men involves the target enzymes of the azoles, which are responsible for the biosynthesis of ergosterol. Resistance may be caused by mutation, increased production of an enzyme, drug efflux mechanisms, or the development of compensatory pathways.

There have been reports of superinfection with Candida species other than C. albicans, which often have inherently not susceptible to fluconazole (e.g. Candida krusei) reduced susceptibility (C. glabrata) or resistance to fluconazole (e.g. C.krusei, C. auris). Such infections may require alternative antifungal therapy.

1.3.1.5.2. Pharmacokinetic properties: [Fluconazole Capsules BP 1 gm]

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. The 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 23.4μg/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 1.8μg/g in diseased nails; and, fluconazole was still measurable in nail samples 6 months after the end of therapy.

Biotransformation

Fluconazole is metabolized 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 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.

Pharmacokinetics in renal impairment

In patients with severe renal insufficiency, (GFR< 20 ml/min) half life increased from 30 to 98 hours. Consequently, reduction of the dose is needed. Fluconazole is removed by haemodialysis and to a lesser extent by peritoneal dialysis. After three hours of haemodialysis session, around 50% of fluconazole is eliminated from blood.

Pharmacokinetics during lactation

A pharmacokinetic study in ten lactating women, who had temporarily or permanently stopped breast-feeding their infants, evaluated fluconazole concentrations in plasma and breast milk for 48 hours following a single 150 mg dose of fluconazole. Fluconazole was detected in breast milk at an average concentration of approximately 98% of those in maternal plasma. The mean peak breast milk concentration was 2.61 mg/L at 5.2 hours post-dose. The estimated daily infant dose of fluconazole from breast milk (assuming mean milk consumption of 150 ml/kg/day) based on the mean peak milk concentration is 0.39 mg/kg/day, which is approximately 40% of the recommended neonatal dose (<2 weeks of age) or 13% of the recommended infant dose for mucosal candidiasis.

Pharmacokinetics in children

Pharmacokinetic data were assessed for 113 paediatric patients from 5 studies; 2 single dose studies, 2 multiple dose studies and a study in premature neonates. Data from 1 study were not interpretable due to changes in formulation pathway through the study. Additional data were available from a compassionate use study.

After administration of 2 - 8 mg/kg fluconazole to children between the ages of 9 months to 15 years, an AUC of about38 μg.h/ml was found per 1 mg/kg dose units. The average fluconazole plasma elimination half-life varied between 15and 18 hours and the distribution volume was approximately 880 ml/kg after multiple doses. A higher fluconazole plasma elimination half-life of approximately 24 hours was found after a single dose. This is comparable with the fluconazole plasma elimination half-life after a single administration of 3 mg/kg i.v. to children of 11 days-11 months old. The distribution volume in this age group was about 950 ml/kg.

Experience with fluconazole in neonates is limited to pharmacokinetic studies in premature newborns. The mean age at first dose was 24 hours (range 9-36 hours) and mean birth weight was 0.9 Kg (range 0.75-1.10 Kg) for 12 pre-termneonates of average gestation around 28 weeks. Seven patients completed the protocol; a maximum of five 6 mg/kg intravenous infusions of fluconazole were administered every 72 hours. The mean half-life (hours) was 74 (range 44-185) on day 1 which decreased with time to a mean of 53 (range 30-131) on day 7 and 47 (range 27-68) on day 13. The area under the curve (microgram.h/ml) was 271 (range 173-385) on day 1 and increased with a mean of 490 (range 292-734) on day 7 and decreased with a mean of 360 (range 167-566) on day 13. The volume of distribution (ml/kg) was1183 (range 1070-1470) on day 1 and increased with time to a mean of 1184 (range 510-2130) on day 7 and 1328(range 1040-1680) on day 13.

Pharmacokinetics in elderly

A pharmacokinetic study was conducted in 22 subjects, 65 years of age or older receiving a single 50 mg oral dose of fluconazole. Ten of these patients were concomitantly receiving diuretics. The Cmax was 1.54 μg/ml and occurred at 1.3hours post-dose. The mean AUC was 76.4 ± 20.3 μgh/ml, and the mean terminal half-life was 46.2 hours. These pharmacokinetic parameter values are higher than analogous values reported for normal young male volunteers. Coadministation of diuretics did not significantly alter AUC or Cmax. In addition, creatinine clearance (74 ml/min), the percent of medicinal product recovered unchanged in urine (0-24 h, 22%) and the fluconazole renal clearance estimates (0.124 ml/min/kg) for the elderly were generally lower than those of younger volunteers. Thus, the alteration of fluconazole disposition in the elderly appears to be related to reduced renal function characteristics of this group.

1.3.1.5.3 Preclinical safety data [Fluconazole Capsules BP 1 gm]

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 pelvisdilation) 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 as light 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

1.3.1.6. Pharmaceutical particulars: [Fluconazole Capsules BP 1 gm]

1.3.1.6.1. List of Excipients:

Tablet core:

- Microcrystalline Cellulose Grade 102
- Sodium Lauryl Sulphate
- Magnesium Stearate
- Colloidal Anhydrous Silica
- Lactose Monohydrate Granulated DCL-15 DC2050
- Lactose Monohydrate
- EHG CAPS "2" Black/ Red

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1.3.1.3. Pharmaceutical form: [Tinidazole Tablets 1 gm]

Dosage Form: Solid oral dosage form- Tablet

Visual & Physical characteristics of the product:
A blue coloured capsule shape, biconvex film coated tablet, having breakline on both sides of the tablet.

1.3.1.4. Clinical particulars [Tinidazole Tablets 1 gm]

1.3.1.4.1. Therapeutic indications:

Treatment of Vaginal discharge or itching resulting from single or multiple infections due to vaginal candidiasis, bacterial vaginosis, trichomoniasis and non-complicated gonorrhea.

1.3.1.4.2. Posology and method of administration: [Tinidazole Tablets 1 gm]

Prophylaxis

Prevention of post-operative infections

Use in Adults:

Oral: A single dose of 2 g approximately 12 hours before surgery

Use in Children less than 12 years:

There is no data available to permit dosage recommendations for prophylaxis of anaerobic infections in children below the age of 12 years.

Treatment

Anaerobic infections

Use in Adults:

Oral: An initial dose of 2 g the first day followed by 1 g daily, given as a single dose or as 500 mg twice daily.

Treatment for 5 to 6 days will generally be adequate, but clinical judgment must be used in determining the duration of therapy, particularly when eradication of infection from certain sites may be difficult.

Routine clinical and laboratory observation is recommended if it is considered necessary to continue therapy for more than 7 days.

Use in Children Less Than 12 Years:

There is no data available to permit dosage recommendations for treatment of anaerobic infections in children below the age of 12 years.

Acute ulcerative gingivitis

Use in Adults:

A single oral dose of 2 g.

Urogenital trichomoniasis

When infection with Trichomonas vaginalis is confirmed, simultaneous treatment of the consort is recommended.

Use in Adults:

Preferred Regimen:

A single oral dose of 2 g.

Use in Children:

A single dose of 50 to 75 mg/kg of body weight. It may be necessary to repeat this dose once in some cases

Giardiasis

Use in Adults:

A single oral dose of 2 g.

Use in Children:
A single dose of 50 to 75 mg/kg of body weight. It may be necessary to repeat this dose once in some cases.

Intestinal amebiasis

Use in Adults:
A single oral daily dose of 2 g for 2 to 3 days. Occasionally, when a three-day single daily dose is ineffective, treatment may be continued for up to six days. When a five-day, twice daily course is ineffective, treatment may be continued for up to 10 days.

Use in Children:
A single dose of 50 to 60 mg/kg of body weight/ day for three successive days.

Amebic involvement of the liver

For amebic involvement of the liver, the aspiration of pus may be required in addition to therapy with tinidazole.

Use in Adults:
Oral: Total dosage varies from 4.5 to 12 g, depending on the virulence of Entamoeba histolytica.
Initiate treatment with 1.5 to 2 g orally as a single daily dose for 3 days. Occasionally, when a three-day course is ineffective, treatment may be continued for up to 6 days.

Use in Children:
A single oral dose of 50 to 60 mg/kg of body weight/ day for five successive days.

Use in Renal Impairment

Dosage adjustments in patients with impaired renal function are generally not necessary. However, because tinidazole is easily removed by haemodialysis, patients may require additional doses of tinidazole to compensate.

Oral Administration

It is recommended that oral tinidazole be taken during or after a meal.

1.3.1.4.3. Contraindications: [Tinidazole Tablets 1 gm]

Hypersensitivity to azole group or nitroimidazole group of compounds, Azithromycin or any other macrolide such as erythromycin. It is contraindication in those patients with a history of blood dyscrasias and epileptic seizures.

1.3.1.4.4. Special warnings and precautions for use: [Tinidazole Tablets 1 gm]

WARNINGS:

Those who develop rashes due to fluconazole (in the Combikit) must be monitored closely. Fluconazole (in the Combikit) needs to be advocated with due precaution along with oral hypoglycemics, coumarins, phenytoin, cyclosporine, rifampicin, theophylline, astemizole, rifabutin, tacrolimus and short-acting benzodiazepines. As azithromycin interacts with aluminium and magnesium-containing antacids, digoxin, ergot derivatives, triazolam and drugs metabolized by cytochrome P450 such as carbamazepine, cyclosporine, phenytoin, the Combikit must be coadministered with care. Alcohol beverages must be avoided whilst taking the Combikit, and for three days thereafter since simultaneous intake of nitroimidazoles like tinidazole could result in abdominal cramps, flushing, nausea, vomiting, headaches and even psychotic reactions.

MODULE 1 – ADMINISTRATIVE PARTICULARS OF THE PRODUCT

PRECAUTIONS:

The Combikit is to be advocated with due precaution in hepatic and renal disease, and potentially proarrhythmic conditions in view potential of fluconazole and azithromycin to induce liver and kidney dysfunction, and cardiac conduction abnormalities.The Combikit should be advocated with care in diarrhea since azithromycin usage could be associated with pseudomembranous colitis.

1.3.1.4.5. Interaction with other medicinal products and other forms of interaction:

Renal impairment: [Tinidazole Tablets 1 gm]

Caution has to be taken.

Hepatic impairment:

Patients who develop abnormal liver function should be monitored.

Anticoagulants:

Fluconazole has been shown to prolong prothrombin time of coumarin drugs, hence requires careful monitoring. Cyclosporine: Concomitant administration of fluconazole and cyclosporine may result in increase in cyclosporine levels. Phenytoin: Fluconazole significantly increases phenytoin levels and A UC resulting in phenytoin toxicity.

Oral hypoglycaemics:

Concomitant administration of fluconazole and oral hypoglycaemics such as sulphonyl urea in diabetic patients results in increased plasma concentrations and reduced metabolism of antidiabetic agents.

Rifampicin:

Concomitant administration of fluconazole and rifampicin decreases A UC of fluconazole by 20%. Theophylline: Fluconazole may increase serum concentrations of theophylline.

Alcohol:

Disulfiram-like antabuse reaction may occur due to tinidazole. Antacids: reduced absorption of Azithromycin.

1.3.1.4.6. Pregnancy and lactation: [Tinidazole Tablets 1 gm]

PREGNANCY

Tinidazole crosses the placental barrier. Since the effects of compounds of this class on fetal development are unknown, the use of tinidazole during the first trimester is contraindicated. There is no evidence that tinidazole is harmful during the latter stages of pregnancy, but its use during the second and third trimesters requires that the potential benefits be weighed against the possible hazards to the mother or fetus.

LACTATION

Tinidazole is distributed into breast milk. Tinidazole may be present in breast milk for more than 72 hours after administration. Women should not nurse during and for at least three days after having discontinued taking tinidazole.

1.3.1.4.7. Effects on ability to drive and use machines: [Tinidazole Tablets 1 gm]

The effect of tinidazole on the ability to drive or use machinery has not been studied. There is no evidence to suggest that tinidazole may affect these abilities.

1.3.1.4.8. Undesirable effects: [Tinidazole Tablets 1 gm]

All ADRs listed in the CDS are presented by MedDRA SOC. Within each frequency category, the ADRs are presented in the order of clinical importance.

MODULE 1 – ADMINISTRATIVE PARTICULARS OF THE PRODUCT

System Organ Class	Common ≥1/100 to <1/10	Frequency Not Known (cannot be estimated from available data)
Blood and the Lymphatic System Disorders		Leukopenia
Immune System Disorders		Drug hypersensitivity
Metabolism and Nutrition Disorders	Decreased appetite	
Nervous System Disorders	Headache	Convulsions Neuropathy peripheral Paraesthesia Hypoaesthesia Sensory disturbances Ataxia Dizziness Dysgeusia
Ear and Labyrinth Disorders	Vertigo	
Vascular Disorders		Thrombophlebitis* Flushing
Gastrointestinal Disorders	Vomiting Diarrhoea Nausea Abdominal pain	Glossitis Stomatitis Tongue discolouration
Skin and Subcutaneous Tissue Disorders	Dermatitis allergic Pruritus Skin Hyperpigmentation	Angioedema Urticaria
Renal and Urinary Disorders		Chromaturia
General Disorders and Administration Site Conditions		Pyrexia Fatigue

CIOMS III categories: Common ≥1/100 to ≤1/10 (≥% and <10%), Not known: frequency cannot be estimated from available data

*Thrombophlebitis has occasionally been observed at the infusion site with the intravenous dosage form.

1.3.1.4.9. Overdose: [Tinidazole Tablets 1 gm]

Signs and Symptoms of Overdose

Reports of overdoses in humans with tinidazole are anecdotal and do not provide consistent data regarding the signs and symptoms of overdose.

Treatment of Overdose

There is no specific antidote for the treatment of overdosage with tinidazole. Treatment is symptomatic and supportive. Gastric lavage may be useful. Tinidazole is easily dialyzable.

1.3.1.5. Pharmacological properties: [Tinidazole Tablets 1 gm]

1.3.1.5.1. Pharmacodynamic properties:

Tinidazole is active against both protozoa and obligate anaerobic bacteria. The activity against protozoa includes Trichomonas vaginalis, Entamoeba histolytica and Giardia lamblia. Tinidazole is active against 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.

MODULE 1 – ADMINISTRATIVE PARTICULARS OF THE PRODUCT

1.3.1.5.2. Pharmacokinetic properties: [Tinidazole Tablets 1 gm]

Absorption: Tinidazole is rapidly and completely absorbed following oral administration. In studies with healthy volunteers receiving 2 g tinidazole orally, peak serum levels of 40-51 mcg/ml were achieved within two hours and decreased to between 11-19 mcg/ml at 24 hours.

Distribution: Tinidazole 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 liters. About 12% of plasma tinidazole is bound to plasma proteins.

Elimination: Tinidazole 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 tinidazole. Up to 5% of the administered dose is excreted in the feces. Studies in patients with renal failure (creatinine clearance <22 ml/min) indicate that there is no statistically significant change in tinidazole pharmacokinetic parameters in these patients

1.3.1.5.3 Preclinical safety data [Tinidazole Tablets 1 gm]

Fertility studies in rats receiving 100 mg or 300 mg tinidazole/kg had no effect on fertility, adult and pup weights, gestation, viability or lactation. There was a slight, not significant, increase in resorption rate at the 300 mg/kg dose. In the study with 60 days duration, NOAEL related with testicular adverse effects and spermatogenesis was 100 mg/kg. In acute animal studies with mice and rats, the LD50 for mice was >3600 mg/kg and >2300 mg/kg for oral and intraperitoneal administration, respectively. For rats, the LD50 was >2000 mg/kg for both oral and intraperitoneal administration. Tinidazole was mutagenic in TA 100, S. typhimurium tester strain both with and without the metabolic activation system and was negative for mutagenicity in the TA 98 strain. Mutagenicity results were mixed (positive and negative) in the TA 1535, 1537, and 1538 strains. Tinidazole was also mutagenic in a tester strain of Klebsiella pneumonia. Tinidazole was negative for mutagenicity in a mammalian cell culture system utilizing Chinese hamster lung V79 cells (HGPRT test system) and negative for genotoxicity in the Chinese hamster ovary (CHO) sister chromatid exchange assay. Tinidazole was positive for in vivo genotoxicity in the mouse micronucleus assay.

1.3.1.6. Pharmaceutical particulars: [Tinidazole Tablets 1 gm]

1.3.1.6.1. List of Excipients:

Tablet core:

- Maize Starch
- Crospovidone
- PVPK 30 (Polyvinyl Pyrrolidone K-30)
- Purified water
- Magnesium Stearate
- Purified Talc
- Colloidal Anhydrous Silica

Coating:

- Dichloromethane
- Denature Absolute Alcohol (DAA) with 0.5 % Acetone

- Col. EZY 17F580022 (White)
- Titanium Dioxide
- Col. Brilliant Blue Lake

1.3.1.3. Pharmaceutical form: [Azithromycin Tablets USP 1 gm]

Dosage Form: Solid oral dosage form- Tablet

Visual & Physical characteristics of the product:
A yellow coloured, capsule shape, biconvex film coated tablets, having breakline on one side of the tablets.

1.3.1.4. Clinical particulars [Azithromycin Tablets USP 1 gm]

1.3.1.4.1. Therapeutic indications:
Treatment of Vaginal discharge or itching resulting from single or multiple infections due to vaginal candidiasis, bacterial vaginosis, trichomoniasis and non-complicated gonorrhea.

1.3.1.4.2. Posology and method of administration: [Azithromycin Tablets USP 1 gm]

Adults
In uncomplicated Chlamydia trachomatis urethritis and cervicitis the dose is 1,000 mg as a single oral dose.
For all other indications the dose is 1,500 mg, to be administered as 500 mg per day for three consecutive days. As an alternative the same total dose (1,500 mg) can also be administered over a period of five days with 500 mg on the first day and 250 mg on the second to the fifth day.

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

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

In patients with renal impairment:
No dose adjustment is necessary in patients with mild to moderate renal impairment(GFR 10-80 ml/min)

In patients with hepatic impairment:
A dose adjustment is not necessary for patients with mild to moderately impairedliver function.

1.3.1.4.3. Contraindications: [Azithromycin Tablets USP 1 gm]
Hypersensitivity to azole group or nitroimidazole group of compounds, Azithromycin or any other macrolide such as erythromycin. It is contraindication in those patients with a history of blood dyscrasias and epileptic seizures.

1.3.1.4.4. Special warnings and precautions for use: [Azithromycin Tablets USP 1 gm]

WARNINGS:

Those who develop rashes due to fluconazole (in the Combikit) must be monitored closely. Fluconazole (in the Combikit) needs to be advocated with due precaution along with oral hypoglycemics, coumarins, phenytoin, cyclosporine, rifampicin, theophylline, astemizole, rifabutin, tacrolimus and short-acting benzodiazepines. As azithromycin interacts with aluminium and magnesium-containing antacids, digoxin, ergot derivatives triazolam and drugs metabolized by cytochrome P450 such as carbamazepine, cyclosporine, phenytoin, the Combikit must be coadministered with care. Alcohol beverages must be avoided whilst taking the Combikit, and for three days thereafter since simultaneous intake of nitroimidazoles like tinidazole could result in abdominal cramps, flushing, nausea, vomiting, headaches and even psychotic reactions.

PRECAUTIONS:

The Combikit is to be advocated with due precaution in hepatic and renal disease, and potentially proarrhythmic conditions in view potential of fluconazole and azithromycin to induce liver and kidney dysfunction, and cardiac conduction abnormalities.The Combikit should be advocated with care in diarrhea since azithromycin usage could be associated with pseudomembranous colitis.

1.3.1.4.5. Interaction with other medicinal products and other forms of interaction:

Renal impairment: [Azithromycin Tablets USP 1 gm]

Caution has to be taken.

Hepatic impairment:

Patients who develop abnormal liver function should be monitored.

Anticoagulants:

Fluconazole has been shown to prolong prothrombin time of coumarin drugs, hence requires careful monitoring. Cyclosporine: Concomitant administration of fluconazole and cyclosporine may result in increase in cyclosporine levels. Phenytoin: Fluconazole significantly increases phenytoin levels and A UC resulting in phenytoin toxicity.

Oral hypoglycaemics:

Concomitant administration of fluconazole and oral hypoglycaemics such as sulphonyl urea in diabetic patients results in increased plasma concentrations and reduced metabolism of antidiabetic agents.

Rifampicin:

Concomitant administration of fluconazole and rifampicin decreases A UC of fluconazole by 20%. Theophylline: Fluconazole may increase serum concentrations of theophylline.

Alcohol

1.3.1.4.6. Pregnancy and lactation: [Azithromycin Tablets USP 1 gm]

PREGNANCY

There are no adequate and well-controlled studies on the use of azithromycin in pregnant women. In reproduction toxicity studies in animals azithromycin was shown to pass the placenta, but no teratogenic effects were observe). The safety of azithromycin has not been confirmed with regard to the use of the active substance during pregnancy. Therefore azithromycin should only be used during pregnancy if the benefit outweighs the risk.

LACTATION

Azithromycin is excreted in breast milk. Because of the long half-life, accumulation in the milk is possible. Information available from published literature indicates that, in short-term

use, this does not lead to clinically relevant quantities in the milk. No serious side effects have been observed by azithromycin in breast-fed children.
A decision should be taken whether breastfeeding is discontinued or that treatment with azithromycin is discontinued/initiated or not, taking into account the benefit of breastfeeding for the child and the benefit of treatment for the woman.

1.3.1.4.7. Effects on ability to drive and use machines: [Azithromycin Tablets USP 1 gm]

There is no evidence to suggest that azithromycin may have an effect: on a patient's ability to drive or operate machinery. Visual impairment and vision blurred may have an effect on a patient's ability to drive or operate machinery

1.3.1.4.8. Undesirable effects: [Azithromycin Tablets USP 1 gm]

The table below lists the adverse reactions identified through clinical experience and post-marketing 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); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

1.3.1.4.9. Overdose: [Azithromycin Tablets USP 1 gm]

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses.

Symptoms

The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea.

Treatment

In the event of overdose the administration of medicinal charcoal and general symptomatic treatment and supportive measures are indicated as required.

1.3.1.5. Pharmacological properties: [Azithromycin Tablets USP 1 gm]

1.3.1.5.1. Pharmacodynamic properties: [Azithromycin Tablets USP 1 gm]

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

Mode of action:

Azithromycin is an azalide, a sub-class of the macrolid antibiotics. 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 of azithromycin.
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

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. 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.

1.3.1.5.2. Pharmacokinetic properties: [Azithromycin Tablets USP 1 gm]

Absorption

After oral administration the bioavailability of azithromycin is approximately 37%. Peak plasma levels are reached after2-3 hours (Cmax after a single dose of 500 mg orally was approximately 0.4 mg/l).

Distribution

Kinetic studies have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the active substance is heavily tissue bound (steady state distribution volume of approximately 31 l/kg). Concentrations in target tissues such as lung, tonsil, and prostate exceed the MIC 90 for likely pathogens after a single dose of 500 mg. In experimental in vitro and in vivo studies azithromycin accumulates in the phagocytes, freeing is stimulated by active phagocytosis. In animal studies this process appeared to contribute to the accumulation of azithromycin in the tissue. In serum the protein binding of azithromycin is variable and depending on the serum concentration varies from 50% in 0.05 mg/l to 12% in 0.5 mg/l.

Excretion

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

Pharmacokinetics in special populations

Renal insufficiency

Following a single oral dose of azithromycin 1 g, mean Cmax and AUC0-120 increased by 5.1% and 4.2% respectively, insubjects with mild to moderate renal impairment (glomerular filtration rate of 10-80 ml/min) compared with normal renalfunction (GFR > 80 ml/min). In subjects with severe renal impairment, the mean Cmax and AUC0-120 increased 61% and33% respectively compared to normal.

Hepatic insufficiency

In patients with mild to moderate hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to normal hepatic function. In these patients, urinary recovery of azithromycin appears to increase perhaps to compensate for reduced hepatic clearance.

Elderly

The pharmacokinetics of azithromycin in elderly men was similar to that of young adults; however, in elderly women, although higher peak concentrations (increased by 30-50%) were observed, no significant accumulation occurred. Infants, toddlers, children and adolescents**.**

1.3.1.5.3 Preclinical safety data [Azithromycin Tablets USP 1 gm]

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

Carcinogenic potential:

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

Mutagenic potential:

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

Reproductive toxicity:

No teratogenic effects were observed in animal studies of embryotoxicity in mice and rats. In rats, azithromycin doses of100 and 200 mg/kg bodyweight/day led to mild retardations in foetal ossification and in maternal weight gain. Inperi-/postnatal studies in rats, mild retardations following treatment with 50 mg/kg/day azithromycin and above were observed.

1.3.1.6. Pharmaceutical particulars: [Azithromycin Tablets USP 1 gm]

1.3.1.6.1. List of Excipients:

Tablet core:

- Micro crystalline Cellulose Powder
- Croscarmellose Sodium
- Sodium Lauryl Sulphate
- Starch 1500
- PVPK 30 (Polyvinyl Pyrrolidone K-30)
- Microcrystalline Cellulose Grade 102
- Colloidal Anhydrous Silica
- Magnesium Stearate

Coating:

- Dichloromethane
- Denature Absolute Alcohol (DAA) with 0.5 % Acetone
- Col.Elegance Coat EL-OY- 8005 Yellow (Iron Oxide of Yellow)

1.3.1.6.2. Incompatibilities:

Not applicable.

1.3.1.6.3. Shelf life: 36 months

1.3.1.6.4. Special precautions for storage:

Store below 30 °C, in a dry place, Protect from light.

MODULE 1 – ADMINISTRATIVE PARTICULARS OF THE PRODUCT

1.3.1.6.5. Nature and contents of container:

Primary packing: 1 Tablet (Azithromycin), 2 Tablets (Tinidazole), 1 Capsule (Fluconazole), in ALU-PVC Blister Pack.

Secondary packing: Such a 01 ALU-PVC Blister pack in monocarton along with package insert.

1.3.1.6.6. Special precautions for disposal:

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

1.3.1.7. Registrant:

Evans Therapeutics Limited.

No. 24, Abimbola Way, Isolo Industrial Estate, Isolo. Lagos, Nigeria

E-mail: olanihun.temitope@evanstherapeutics.com

1.3.1.8. Manufacturer:

BHARAT PARENTERALS LTD.

Name	**:**	**Bharat Parenterals Ltd.**
Address	**:**	144 & 146, Jarod Samlaya Road, Vill. Haripura, Ta. Savli, Dist. Vadodara – 391520, Gujarat INDIA.
Telephone Number	**:**	+91-2667-251669, 251670, 251679, 251680
Fax Number	**:**	+91-2667-251679, 251680
E-mail	**:**	bplbrd@yahoo.com, info@bplindia.in, bplbrd@bplindia.in.

1.3.1.9. Date of revision of the text:

1.3.1.10. Instructions for Preparation of Radiopharmaceuticals (If Applicable):

Not Applicable