National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

AD-FLUCONAZOLE 150 (Fluconazole Tablets USP 150 mg)

2. QUALITATIVE AND QUANTITATIVECOMPOSITION

Each uncoated tablets contains:

Fluconazole USP……150 mg

Excipients……..q.s

List of Excipients:

Excipients	Quantity /Tablet (mg)	Uses
SHIFTING/MIXING		
Lactose	135.000	Diluent
Cross carmellose sodium	20.000	Disintegrant
Microcrystalline Cellulose (Plain)	132.000	Diluent
GRANULATION		
PVPK 30	15.000	Binder
Lubrication		
Colloidal Silicon Dioxide (Light)	4.000	Lubricant
Sodium Lauryl sulphate	8.000	Surfactant
Magnesium stearate	6.000	Lubricant
Cross carmellose sodium (vivasole)	20.000	Disintegrant

3. PHARMACEUTICAL FORM

White colour caplet shape uncoated tablet having both side plain.

4. Clinical particulars

4.1 Therapeutic indications

Fluconazole is indicated in the following fungal infections

Fluconazole is indicated in adults for the treatment of:

- Cryptococcal meningitis
- Coccidioidomycosis
- Invasive candidiasis
- Mucosal candidiasis including oropharyngeal, oesophageal candidiasis, candiduria and chronic mucocutaneous candidiasis
- Chronic oral atrophic candidiasis (denture sore mouth) if dental hygiene or topical treatment are insufficient
- Vaginal candidiasis, acute or recurrent; when local therapy is not appropriate
- Candidal balanitis when local therapy is not appropriate
- Dermatomycosis including *tinea pedis*, *tinea corporis*, *tinea cruris*, *tinea versicolor* and dermal *candida* infections when systemic therapy is indicated

  Tinea unguinium (onychomycosis) when other agents are not considered appropriate

4.2 Posology and method of administration

Posology

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.

Indications		**Posology**	**Duration of treatment**
Cryptococcosis	- Treatment of cryptococcal meningitis.	Loading dose: 400 mg on Day 1 Subsequent dose: 200 mg to 400 mg daily	Usually at least 6 to 8 weeks. In life threatening infections the daily dose can be increased to 800 mg
	- Maintenance therapy to prevent relapse of cryptococcal meningitis in patients with high risk of recurrence.	200 mg daily	Indefinitely at a daily dose of 200 mg
Coccidioidomycosis		200 mg to 400 mg	11 months up to 24 months or longer depending on the patient. 800 mg daily may be considered for some infections and especially for meningeal disease
Invasive candidiasis		Loading dose: 800 mg on Day 1 Subsequent dose: 400 mg daily	In general, the recommended duration of therapy for candidemia is for 2 weeks after first negative blood culture result and resolution of signs and symptoms attributable to candidemia.
Treatment of mucosal candidiasis	-Oropharyngeal candidiasis	Loading dose: 200 mg to 400 mg on Day 1 Subsequent dose: 100 mg to 200 mg daily	7 to 21 days (until oropharyngeal candidiasis is in remission). Longer periods may be used in patients with severely compromised immune function
	Oesophageal candidiasis	Loading dose: 200 mg to 400 mg on Day 1 Subsequent dose: 100 mg to 200 mg daily	14 to 30 days (until oesophageal candidiasis is in remission). Longer periods may be used in patients with severely compromised immune function
	Candiduria	200 mg to 400 mg daily	7 to 21 days. Longer periods may be used in patients with severely compromised immune function.
	Chronic atrophic candidiasis	50 mg daily	14 days
	Chronic mucocutaneous candidiasis	50 mg to 100 mg daily	Up to 28 days. Longer periods depending on both the severity of infection or underlying immune compromisation and infection
Prevention of relapse of mucosal candidiasis in	Oropharyngeal candidiasis	100 mg to 200 mg daily or 200 mg 3 times per week	An indefinite period for patients with chronic immune suppression

patients infected with HIV who are at high risk of experiencing relapse	Oesophageal candidiasis	100 mg to 200 mg daily or 200 mg 3 times per week	An indefinite period for patients with chronic immune suppression
Genital candidiasis	Acute vaginal candidiasis Candidal balanitis	150 mg	Single dose
	Treatment and prophylaxis of recurrent vaginal candidiasis (4 or more episodes a year).	150 mg every third day for a total of 3 doses (day 1, 4, and 7) followed by 150 mg once weekly maintenance dose	Maintenance dose: 6 months.
Dermatomycosis	- *tinea pedis,* - *tinea corporis,* - *tinea cruris,* - *candida* infections	150 mg once weekly or 50 mg once daily	2 to 4 weeks, *tinea pedis*may require treatment for up to 6 weeks
	- *tinea versicolor*	300 mg to 400 mg once weekly	1 to 3 weeks
		50 mg once daily	2 to 4 weeks
	Tinea unguium(*onychomycosis*)	150 mg once weekly	Treatment should be continued until infected nail is replaced (uninfected nail grows in). Regrowth of fingernails and toenails normally requires 3 to 6 months and 6 to 12 months, respectively. However, growth rates may vary widely in individuals, and by age. After successful treatment of long-term chronic infections, nails occasionally remain disfigured.
Prophylaxis of candidal infections in patients with prolonged neutropenia		200 mg to 400 mg	Treatment should start several days before the anticipated onset of neutropenia and continue for 7 days after recovery from neutropenia after the neutrophil count rises above 1000 cells per mm^3.

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4.3 Contraindications

Hypersensitivity to the active substance, to related azole substances, or to any of the excipients.

Coadministration of terfenadine is contraindicated 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, amiodarone and erythromycin are contraindicated in patients receiving fluconazole.

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4.4 Special warning and precautions for use .

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, Fluconazole 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. During post-marketing surveillance, there have been very rare cases of QT prolongation and *torsades de pointes* in patients taking Fluconazole. These reports included seriously ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant treatment that may have been contributory.

Fluconazole should be administered with caution to patients with these potentially proarrhythmic conditions. Coadministration of other medicinal products known to prolong the QT interval and which are metabolised 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 potent CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole is also an inhibitor of CYP2C19. Fluconazole treated patients who are concomitantly treated with medicinal products with a narrow therapeutic window metabolised 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

Adrenal insufficiency

Ketoconazole is known to cause adrenal insufficiency, and this could also although rarely seen be applicable to fluconazole.

Excipients

Capsules contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Amiodarone: Concomitant administration of fluconazole with amiodarone may result in inhibition of amiodarone metabolism. Use of amiodarone has been associated with QT prolongation. Co-administration of fluconazole and amiodarone is contraindicated.

Cisapride: There have been reports of cardiac events including Torsade de Pointes in patients to whom fluconazole and cisapride were coadministered. A controlled study found that concomitant fluconazole 200 mg once daily and cisapride 20 mg four times a day yielded a significant increase in cisapride plasma levels and prolongation of QT interval. 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. One study at a 200 mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400 mg and 800 mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400 mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of fluconazole at doses of 400 mg or greater with terfenadine is contraindicated. The coadministration 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 *torsade depointes*. Coadministration 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 torsade de pointes. Coadministration 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*. Coadministration 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. Coadministration of fluconazole and erythromycin is contraindicated.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There have been reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, 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 hundred pregnant women treated with standard doses (<200 mg/day) of fluconazole, administered as a single or repeated dose in the first trimester, show no increased risk of undesirable effects in the foetus.

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.

Breast-feeding

Fluconazole passes into breast milk to reach concentrations lower than those in plasma. Breast-feeding may be maintained after a single use of a standard dose 200 mg fluconazole or less. Breast-feeding is not recommended after repeated use or after high dose fluconazole.

Fertility

Fluconazole did not affect the fertility of male or female rats

4.7 Effects on ability to drive and use machine

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.

4.8 Undesirable effects

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.

The following adverse reactions have been observed and reported during treatment with Fluconazole with the following frequencies: 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).

System Organ Class	Common	Uncommon	Rare
Blood and the lymphatic system disorders		Anaemia	Agranulocytosis, leukopenia, thrombocytopenia, neutropenia
Immune system disorders			Anaphylaxis
Metabolism and nutrition disorders		Decreased appetite	Hypercholesterolaemia, hypertriglyceridaemia, hypokalemia
Psychiatric disorders		Somnolence, insomnia	
Nervous system disorders	Headache	Seizures, paraesthesia, dizziness, taste perversion	Tremor
Ear and labyrinth disorders		Vertigo	
Cardiac disorders			Torsade de pointes,QT prolongation
Gastrointestinal disorders	Abdominal pain, vomiting, diarrhoea, nausea	Constipation dyspepsia, flatulence, dry mouth	
Hepatobiliary	Alanine aminotransferase	Cholestasis , jaundice ,	Hepatic failure,

disorders	increased , aspartate aminotransferase increased , blood alkaline phosphatase increased	bilirubin increased	hepatocellular necrosis , hepatitis , hepatocellular damage
Skin and subcutaneous tissue disorders	Rash	Drug eruption* , urticaria , pruritus, increased sweating	Toxic epidermal necrolysis, , Stevens-Johnson syndrome , acute generalised exanthematous-pustulosis , dermatitis exfoliative, angioedema, face oedema, alopecia
Musculoskeletal and connective tissue disorders		Myalgia	
General disorders and administration site conditions		Fatigue, malaise, asthenia, fever	

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4.9 Overdose and treatment

There have been reports of overdose with Fluconazole and hallucination and paranoid behaviour have been concomitantly reported.

In the event of overdose, symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate.

Fluconazole is largely excreted in the urine; forced volume diuresis would probably increase the elimination rate. A three-hour haemo dialysis session decreases plasma levels by approximately 50%.

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5- Pharmacological Properties:

5.1 Pharmacodynamic Properties:

ATC classification

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives,

ATC code: J02AC01.

Mode of action

Fluconazole is a triazole antifungal agent. Its primary mode of action is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the 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*

I*n 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*.

PK/PD relationship

In animal studies, there is a correlation between MIC values and efficacy against experimental mycoses due to *Candida* spp. 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 candidaemia to treatment. Similarly cure is less likely for infections caused by strains with a higher fluconazole MIC.

Mechanism(s) 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.

There have been reports of superinfection with *Candida* species other than *C. albicans*, which are often inherently not susceptible to fluconazole (e.g. *Candida krusei*). Such cases may require alternative antifungal therapy.

Breakpoints (according to EUCAST)

Based on analyses of pharmacokinetic/pharmacodynamic (PK/PD) data, susceptibility *in vitro* and clinical response EUCAST-AFST (European Committee on Antimicrobial susceptibility Testing-subcommittee on Antifungal Susceptibility Testing) has determined breakpoints for fluconazole for *Candida* species (EUCAST Fluconazole rational document (2007)-version 2). These have been divided into non-species related breakpoints; which have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species, and species related breakpoints for those species most frequently associated with human infection. These breakpoints are given in the table below:

Antifungal	Species-related breakpoints (S≤/R>)	Non-species related breakpoints[A] S≤/R>

	Candida albicans	*Candida glabrata*	*Candida krusei*	*Candida parapsilosis*	*Candida tropicalis*	
Fluconazole	2/4	IE	--	2/4	2/4	2/4

S = Susceptible, R = Resistant
A = Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints.
-- = Susceptibility testing not recommended as the species is a poor target for therapy with the medicinal product.
IE = There is insufficient evidence that the species in question is a good target for therapy with the medicinal product

5.2 Pharmacokinetic Properties

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, is 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 selective inhibitor of the isozymes CYP2C9 and CYP3A4 (see section 4.5). Fluconazole is also an inhibitor of the isozyme CYP2C19.

Excretion

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

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 27 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 fluconazol.

5. PHARMACEUTICAL PARTICULARS

5.1 List ofexcipients

Dibasic Calcium Phosphate
Maize starch
PVPK – 30
Purified water
Micro crystalline cellulose
Sodium Starch Glycolate
Magnesium Stearate
Purified talc

5.2 Incompatibilities

Not applicable.

5.3 Shelflife

36 months from the date of manufacture

5.4 Special precautions forstorage

Store below 30^0C. Protect from moisture & direct sunlight.

5.5 Nature and contents of container <and special equipment foruse, administrationor implantation>

10 Tablets packed in one Alu -Alu blister. Such 10 blisters packed in unit printed duplex board carton along with its package insert. Such cartons packed in export worthy shipper.

Note: All pack style may not be marketed.

5.6 Special precautions for disposal

No special requirements.

6. MANUFACTURER

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