SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CYTCAN IV (Fluconazole injection USP)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 ml contains:

Fluconazole USP ..... 0.2 gm

Sodium chloride USP ..... 0.9 gm

Water for Injections USP ..... q.s.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion. Sterile, Clear and Colourless to Slightly Yellow Solution filled in FFS 100 ml Plastic Bottle.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluconazole Injection, USP is indicated 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/topical treatment are insufficient.

CYTCAN IV is indicated in adults for the prophylaxis of:

- Relapse of cryptococcal meningitis in patients with high risk of recurrence.
- Relapse of oropharyngeal or oesophageal candidiasis in patients infected with HIV who are at high risk of experiencing relapse.
- Prophylaxis of candidal infections in patients with prolonged neutropenia such as patients with haematological malignancies receiving chemotherapy or patients receiving Hematopoietic Stem Cell Transplantation (see section 5.1).

CYTCAN IV is indicated in term newborn infants, infants, toddlers, children and adolescents aged from 0 to 17 years old for the treatment of mucosal candidiasis (oropharyngeal, oesophageal), invasive candidiasis, cryptococcal

meningitis and the prophylaxis of candidal infections in immunocompromised patients. CYTCAN IV can be used as maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of reoccurrence (see section 4.4).

Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

4.2 Posology and method of administration

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.

Adults

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.
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 patients infected with HIV who are at high risk of experiencing relapse:

- Oropharyngeal candidiasis: 100 mg to 200 mg daily or 200 mg 3 times per week. An indefinite period for patients with chronic immune suppression.
- Oesophageal candidiasis: 100 mg to 200 mg daily or 200 mg 3 times per week. An indefinite period for patients with chronic immune suppression.

Prophylaxis of candidal infections

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/mm3.

Special populations

Elderly

Dosage should be adjusted based on the renal function.

Renal impairment

CYTCAN IV 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 renal function who will receive multiple doses of fluconazole, an initial dose of 50 mg to 400 mg should be given, based on the recommended daily dose for the indication. After this initial loading dose, the daily dose according to indication should be based on the following table:

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

Patients on regular dialysis should receive 100% of the recommended dose after each dialysis; on non-dialysis days, 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 (see sections 4.4 and 4.8).

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. CYTCAN IV 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.

Indication (Infants, toddlers and children 28 days to 11 years)	Posology	Recommendations
Mucosal candidiasis	Initial dose: 6 mg/kg. Subsequent dose: 3 mg/kg daily.	Initial dose may be used on the first day to achieve steady state levels more rapidly.
Invasive candidiasis / Cryptococcal meningitis	6 to 12 mg/kg daily	Depending on the severity of the disease.
Maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of recurrence	6 mg/kg daily	Depending on the severity of the disease.
Prophylaxis of Candida in immunocompromised patients	3 to 12 mg/kg daily	Depending on the extent and duration of the induced neutropenia (see Adults posology).

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.

Term newborn infants (0 to 27 days): Neonates excrete fluconazole slowly. There are few pharmacokinetic data to support this posology in term newborn infants (see section 5.2).

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 72 hours should not be exceeded.
Term newborn infants 15 to 27 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 48 hours should not be exceeded.

Method of Administration

Route of Administration: Intravenous infusion should be administered at a rate not exceeding 10 ml/minute. CYTCAN IV is available as a dilute sodium chloride solution; in patients requiring sodium or fluid restriction, consideration should be given to the rate of fluid administration.

4.3 Contraindications

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

Coadministration of terfenadine is contraindicated in patients receiving CYTCAN IV at multiple doses of 400 mg per day or higher based upon results of a multiple dose interaction study.

Coadministration 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.

4.4 Special warnings 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

CYTCAN IV should be administered with caution to patients with renal dysfunction (see section 4.2).

Adrenal insufficiency

Ketoconazole is known to cause adrenal insufficiency, and this could also (although rarely seen) be applicable to fluconazole. Adrenal insufficiency relating to concomitant treatment with prednisone is described in section 4.5 (The effect of fluconazole on other medicinal products).

Hepatobiliary system

CYTCAN IV should be administered with caution to patients with liver dysfunction. CYTCAN IV 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 with 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 CYTCAN IV. 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. CYTCAN IV 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 (see sections 4.3 and 4.5).

Halofantrine

Halofantrine has been shown to prolong the QTc interval at the recommended therapeutic dose and is a substrate of CYP3A4. The concomitant use of fluconazole and halofantrine is therefore not recommended (see section 4.5).

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 (see section 4.3).

Cytochrome P450

Fluconazole is a potent CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole is also an inhibitor of CYP2C19. CYTCAN IV treated patients who are concomitantly treated with medicinal products with a narrow therapeutic window metabolised through CYP2C9, CYP2C19 and CYP3A4, should be monitored (see section 4.5).

Terfenadine

The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored (see sections 4.3 and 4.5).

Excipients

This medicinal product contains 0.154 mmol sodium per ml. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Fluconazole is a potent CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole is also an inhibitor of CYP2C19. In addition to the observed/documented interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolised by CYP2C9 and CYP3A4 co-administered with fluconazole. Caution should therefore be exercised when using these combinations and patients should be monitored closely. The enzyme inhibiting effect of fluconazole persists 4 to 5 days after

discontinuation of fluconazole treatment due to the long half-life of fluconazole (see section 4.3).

4.6 Fertility, pregnancy and lactation

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 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. 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 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.

4.7 Effects on ability to drive and use machines

No studies have been performed on the effects of CYTCAN IV on the ability to drive or use machines. Patients should be warned about the potential for dizziness or seizures (see section 4.8) while taking CYTCAN IV 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 CYTCAN IV 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 (see section 4.4), QT prolongation (see section 4.4)
Gastrointestinal disorders	Abdominal pain, vomiting, diarrhoea, nausea	Constipation, dyspepsia, flatulence, dry mouth	
Hepatobiliary disorders	Alanine aminotransferase increased (see section 4.4), aspartate aminotransferase increased (see section 4.4), blood alkaline phosphatase	Cholestasis (see section 4.4), jaundice (see section 4.4), bilirubin increased (see section 4.4)	Hepatic failure (see section 4.4), hepatocellular necrosis (see section 4.4), hepatitis (see section 4.4), hepatocellular

	increased (see section 4.4)		damage (see section 4.4)
Skin and subcutaneous tissue disorders	Rash (see section 4.4)	Drug eruption (see section 4.4), urticaria (see section 4.4), pruritus, increased sweating	Toxic epidermal necrolysis (see section 4.4), Stevens-Johnson syndrome (see section 4.4), acute generalised exanthematous pustulosis (see section 4.4), dermatitis exfoliative, angioedema, face oedema, alopecia
Musculoskeletal and connective tissue disorders		Myalgia	
General disorders and administration site conditions		Fatigue, malaise, asthenia, fever including Fixed Drug Eruption	

Paediatric population

The pattern and incidence of adverse reactions and laboratory abnormalities recorded during paediatric clinical trials are comparable to those seen in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS): https://pv.pharmacyboardkenya.org

4.9 Overdose

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 haemodialysis session decreases plasma levels by approximately 50%.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 affect 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 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 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% of the corresponding plasma levels.

Biotransformation

Fluconazole is metabolised only to a minor extent. Of a radioactive dose, only 11% is excreted in a changed form in the urine. Fluconazole is a selective inhibitor of the isozymes CYP2C9 and CYP3A4 (see section 4.5). Fluconazole is also an inhibitor of the isozyme CYP2C19.

Elimination

Plasma elimination half-life for fluconazole is approximately 30 hours. The major route of excretion is renal, with approximately 80% of the administered dose appearing in the urine as unchanged 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, around 50% of fluconazole is eliminated from blood.

Pharmacokinetics in children

Pharmacokinetic data were assessed for 113 paediatric patients from 5 studies. After administration of 2-8 mg/kg fluconazole to children between the ages of 9 months to 15 years, an AUC of about 38 µg·h/ml was found per 1 mg/kg dose units. The average fluconazole plasma elimination half-life varied between 15 and 18 hours and the distribution volume was approximately 880 ml/kg after multiple doses.

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. The Cmax was 1.54 µg/ml and occurred at 1.3 hours post-dose. The mean AUC was 76.4±20.3 µg·h/ml, and the mean terminal half-life was 46.2 hours. Thus, the alteration of fluconazole disposition in the elderly appears to be related to reduced renal function characteristic of this group.

5.3 Preclinical safety data

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. 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 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. Foetal anatomical variants were observed at 25 and 50 mg/kg and higher. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Fluconazole USP
- Sodium Chloride USP
- Water for Injections USP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 30°C in dry place.

6.5 Nature and contents of container

100 ml FFS Plastic bottle. Such 100 ml FFS Plastic bottle is packed in printed carton along with package insert.

6.6 Special precautions for disposal and other handling

Do not use if found leaking upon squeezing or solution is not clear; solution containing visible solid particles must not be used.

7. MARKETING AUTHORISATION HOLDER

Signature Healthcare Limited

Cape Business Park, Along Thika Super Highway, P.O. Box 66172-00800, Nairobi, KENYA.

8. MARKETING AUTHORISATION NUMBER(S)

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