Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Unizol 200mg/100ml Solution for Infusion

2. Qualitative and quantitative composition

Bag contains 200mg of Fluconazole as active substance.

3. Pharmaceutical form

Solution for infusion.

4. Clinical particulars

4.1 Therapeutic indications

It is an ANTIMYCOTIC FOR SYSTEMIC USE

It fights against the development of microscopic fungi; this medicine is recommended in the treatment of:

In Adults:

- Neuromeningeal cryptococcosis.
- Systemic, esophageal and urinary candidiasis.

In Children:

- Oropharyngeal candidiasis in the immunocompromised.
- Systemic, esophageal and urinary candidiasis.
- Neuromeningeal cryptococcosis.

This medicine is also recommended in the prevention of candida infections susceptible in adult leukemia patients who suffer from a decrease in white blood cell count following the treatment received.

4.2 Posology and method of administration

- **Adults:**
- Cryptococcosis: 400 mg/d for 6-8 weeks then 200 mg/d (life-long in patients with AIDS).
- Esophageal candidiasis: 100 mg/d.
- Urinary candidiasis: 100 to 200 mg/d.

- Systemic candidiasis: 800 mg in the 1st day then 400 mg/d.

Prevention of candidiasis:

400mg/d a single daily dose. Started from the initiation of chemotherapy or transplant conditioning, the administration should be continued until seven days after the rise in rates of polymorphonuclear neutrophils above 1000 / mm3 or for a longer duration (up to 75 days).

Children and infants:

- Oropharyngeal candidiasis in the immunocompromised: 3 mg/kg/d every 24 hours.
- Systemic, esophageal and urinary candidiasis: 6-12 mg/ kg/d every 24 hours.
- Neuromeningeal cryptococcosis: 6-12 mg/kg/d every 24 hours (life-long in patients with AIDS). No dosage is proposed in premature infants, full term newborns and up to 28 days of life.

Method and/or route of administration

Intravenous infusion.

Duration of treatment

The duration of treatment depends on clinical response.

If you have used more Fluconazole 2 mg/ml, solution for infusion than you should:

Consult your doctor or pharmacist immediately.

If you forget to take **Fluconazole** 2 mg/ml, solution for infusion:

Do not take a double dose to make up for the single dose that you forgot to take.

4.3 Contraindications

Never use Fluconazole 2 mg/ ml, solution for infusion in the following cases:

- In case of allergy to this drug or related derivatives.
- During pregnancy and lactation, except upon medical advice.
- In combination with:

- Cisapride (medication used for gastroesophageal reflux).
- Pimozide (medication used for certain mood disorders).

This medicine SHOULD NOT GENERALLY BE USED in combination with halofantrine (medication used for the treatment of malaria).

4.4 Special warnings and precautions for use

Be careful with Fluconazole 2 mg/ ml, solution for infusion in the following cases:

- in women of child-bearing age, contraception is essential.
- in patients with cardiac rhythm disorders.
- In case of occurrence of symptoms suggestive of severe liver injury (significant fatigue, anorexia, persistent nausea, vomiting, jaundice), you should consult a doctor.
- if you have previously had skin reaction associated with the use of fluconazole or any other azole derivatives, in case of occurrence of bullous lesions, you should consult a doctor as soon as possible.
- The azole antifungal agents, including fluconazole, have been associated with prolongation of QT interval on the electrocardiogram.
- This medicine contains sodium. This medicine contains 3.54 mg of sodium/ml of solution for injection, To be taken into account in patients controlling their sodium intake.

4.5 Interaction with other medicinal products and other forms of interaction

This medicine should not be used in combination with cisapride (medication used for gastroesophageal reflux), pimozide (medication used for certain mood disorders).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medication, especially halofantrine (medication used for the treatment of malaria) even the medicines obtained without prescription.

4.6 Pregnancy and Lactation

Pregnancy

This medicine should not be used during pregnancy, except upon medical advice. Seek the advice of your doctor or pharmacist before taking any medication.

Lactation

This medicine should not be used during breastfeeding, except upon medical advice. Seek the advice of your doctor or pharmacist before taking any medication.

4.7 Effects on ability to drive and use machines

NA

4.8 Undesirable effects

Like all medicines, **Fluconazole** 2 mg/ml, solution for infusion is likely to have undesirable effects, although not everyone is affected.

The gastrointestinal and cutaneous undesirable effects are the most common.

- Gastrointestinal disorders: nausea, flatulence, abdominal pain, diarrhea.
- Skin and tissue disorders: rash, severe skin reactions. Some cases of generally reversible hair loss have been reported.
- Nervous system disorders: headaches.
- Hepatobiliary disorders: elevated hepatic transaminase (liver enzymes) generally reversible when treatment is discontinued, severe liver injury.
- Blood and lymphatic system disorders: leucopenia (insufficient amount of white blood cells), thrombocytopenia (abnormal low platelet count, essential blood clotting elements).
- Immune system disorders: allergic reaction.
- Cardiac disorders: rare cases of QT interval prolongation and torsade de pointes.

If you notice any undesirable effects not listed in this leaflet, or if certain undesirable effects get serious; please inform your doctor or pharmacist.

4.9 Overdose

N/A

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC code: J02AC01

Mechanism of action

Like other imidazole-and triazole-class antifungals, fluconazole inhibits the fungal cytochrome P450 enzyme 14α-demethylase. Mammalian demethylase activity is much less sensitive to fluconazole than fungal demethylase. This inhibition prevents the conversion of lanosterol to ergosterol, an essential component of the fungal cytoplasmic membrane, and subsequent accumulation of 14α-methyl sterols. Fluconazole is primarily fungistatic; however, it may be fungicidal against certain organisms in a dose-dependent manner, specifically *Cryptococcu*.

5.2 Pharmacokinetic properties

Absorption:

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral route.

Fluconazole is well absorbed after oral intake. The absolute bioavailability is above 90%. Oral absorption is not affected by concomitant food intake. The maximum fasting plasma concentration is reached 0.5-1.5 hours after dose intake. 90% of the steady-state level is reached 4-5 days after dosing once daily.

Plasma concentration is proportional to the dose. After administration of 200 mg of fluconazole, C_{max} is around 4.6 mg/l and plasma concentrations at steady-state after 15 days are around 10 mg/l. After administration of 400 mg of fluconazole, C_{max} is around 9 mg/l and plasma concentrations at steady-state after 15 days are around 18 mg/l. Intake of a double dose on Day 1 results in plasma concentrations of approximately 90% of steady-state on Day 2.

Distribution:

The apparent volume of distribution of fluconazole corresponds 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 the fluconazole levels in the CSF are about 80% of the corresponding plasma levels.

In the stratum corneum, epidermis-dermis and exocrine sweat higher concentrations of fluconazole are reached compared with those in serum. Fluconazole accumulates in the stratum corneum. For example, at a dose of 150 mg once weekly, the concentration of fluconazole in stratum corneum after two doses was 23.3 microgrammes/g and seven days after the end of treatment it was still 7.1 microgrammes/g.

Biotransformation:

Breakdown of fluconazole is modest. Only 11% of a radioactive dose is excreted in the urine as metabolites.

Elimination:

The major route of excretion is renal. Approximately 80% of the dose excreted in the urine in the non-metabolised form. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites.

The average plasma half-life is about 30 hours. The long plasma half-life provides the basis for treatment with single daily doses in all indications.

Paediatric population

Children eliminate fluconazole more rapidly than adults do.

In children (after the neonatal phase) and adolescents of 5-15 years of age the plasma half-life is between 15.2 - 17.6.

Premature babies have a shorter plasma half-life (about 70 hours) and a larger volume of distribution (1.2-2.3 litres/kg) than babies born at full term. During the first week after birth and in the course of the neonatal period, plasma Fluconazole clearance rises (and the plasma half-life falls).

The pharmacokinetics of fluconazole has not been studied in children with renal insufficiency.

Elderly:

A pharmacokinetic study was conducted in 22 subjects, 65 years of age or older receiving a single 50mg oral dose of fluconazole. Ten of these patients were concomitantly receiving diuretics. The Cmax was 1.54µg/ml and occurred at 1.3 hours post-dose. The mean AUC was 76.4±20.3µg•h/ml, and the mean terminal half-life was 46.2 hours. These pharmacokinetics parameter values are higher than analogous values reported for normal young male volunteers. Co-administration of diuretics did not significantly alter AUC or Cmax. In addition, creatinine clearance (74ml/min), the percent of medicinal product recovered unchanged in urine (0-24hr, 22%) and the fluconazole renal clearance estimates (0.124ml/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.

Renal impairment:

In patients with severe renal insufficiency, (GFR<20ml/min) half life increased from 30 to 98 hours. Consequently, reduction of 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.

5.3 Preclinical safety data

Preclinical data from conventional studies on repeat-dose/general toxicity, genotoxicity or carcinogenicity indicate no special hazard for humans not already considered in other sections of the SPC.

Carcinogenesis:

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

In reproduction toxicity studies in rat an increased incidence of hydronephrosis and extension of renal pelvis was reported and embryonal lethality was increased. An increase in anatomical variations and delayed ossification was noted as well as prolonged delivery and dystocia. In reproduction toxicity studies in rabbits abortions were recorded.

6. Pharmaceutical Particulars

6.1 List of Excipients

Sodium Chloride, Sodium hydroxide & water for injection.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3 Shelf-Life

2 years

6.4 Special Precautions for storage

Do not store above 30°C, do not refrigerate & do not freeze.

6.5 Nature and Content of container

Polyolefin bag 100ml closed with a plug then packed in Aluminum pouch along with the insert and label.

6.6 Special precautions for disposal and other handling

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

The product should be inspected visually for particles and discoloration prior to administration. Only clear and colourless solution should be used.

Fluconazole 2mg/ml solution for infusion is compatible with the following infusion fluids:

a. glucose 20% when available

b. Ringer's solution when available

c. Hartmann's solution when available

d. Potassium chloride in glucose when available

e. sodium carbonate 4.2% when available

f. 0.9% sodium chloride (isotonic saline) when available

Compatibility has only been shown for short duration (10 minutes).

Dilution of Fluconazole 2mg/ml solution for infusion is not required prior to administration. If necessary, Fluconazole and the solutions mentioned above should be administered through separate infusion containers. The two reservoirs should be connected using a "Y" connection. The two solutions are then mixed in a single line and the administration is performed. The above method is recommended in order to avoid effects such as the “layering effect” if the two solutions were mixed in one infusion container for the total period of the administration.

7. Marketing Authorization Holder

MS Pharma – Jordan

King Abdullah (II) Bin Al-Hussein Industrial Estate, Amman Jordan Telephone +962 6 40 20 680

Fax +962 6 40 20 679

8. Marketing Authorization Number

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9. Date of first authorization/renewal of the authorization

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10. Date of revision of the text

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