Fluconazole 2 mg/ml solution for infusion

(fluconazole)

PL 24780/0003

UKPAR

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LUAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Villerton Invest S.A. a Marketing Authorisation (licence) for the medicinal product Fluconazole 2mg/ml Solution for Infusion (PL 24780/0003) on 22nd February 2010. This is a prescription-only medicine (POM).

Fluconazole 2mg/ml Solution for Infusion contains the active substance fluconazole, which belongs to a group of medicines called antifungal agents. Fluconazole is used to treat infections caused by fungi or yeasts. It may also be used to prevent you from getting a fungal infection.

You may be given Fluconazole by your doctor to treat fungal infections such as:

- Thrush of the mouth or throat (mucosal infections). Thrush is commonly caused by a yeast called Candida
- Internal (systemic) fungal infections caused by Candida, e.g. infections of the blood stream, urinary tract or other body organs
- Internal (systemic) fungal infections caused by Cryptococcus e.g. cryptococcal meningitis and infections of other sites such as the lungs
- Fungal infections of the skin e.g. ringworm, athlete's foot
- Genital Candida infections e.g. vaginal thrush or candidal balantis (inflammation of the end of the penis and/or foreskin)

You may also be given this medicine to:

- Stop you from getting a fungal infection if your immune system is not working properly
- Stop an infection caused by Cryptococcus coming back (in AIDS patients)

This application is based on a reference product with a valid UK licence. No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of Fluconazole 2mg/ml Solution for Infusion outweigh the risks; hence a Marketing Authorisation has been granted.
Fluconazole 2 mg/ml solution for infusion

(fluconazole)

PL 24780/0003

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Villerton Invest S.A. a Marketing Authorisation for the medicinal product Fluconazole 2mg/ml Solution for Infusion (PL 24780/0003) on 22nd February 2010. The product is a prescription-only medicine (POM).

The application was submitted as a national, abridged application, according to Article 10.1 of Directive 2001/83/EC, as amended. The application makes reference to the innovator product, Diflucan Intravenous Infusion 2mg / ml (PL 00057/0315), authorised to Pfizer Ltd on 31st August 1989. The innovator product has been authorised in the UK for more than 10 years, so the period of data exclusivity has expired.

The active ingredient, fluconazole, belongs to the triazole class of antifungicides, with a mainly fungistatic action. It is a potent and selective inhibitor of fungal enzymes necessary for the synthesis of ergosterol. Fluconazole is very specific for fungal cytochrome P450 dependent enzymes.

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

Fluconazole 2 mg/ml Solution for Infusion is indicated in the following:

1. Genital candidiasis. Vaginal candidiasis, acute or recurrent. Candidal balantis. The treatment of partners who present with symptomatic genital candidiasis should be considered.

2. Mucosal candidiasis. These include oropharyngeal, oesophageal non-invasive bronchopulmonary infections, candiduria, mucocutaneous and chronic oral atrophic candidiasis (associated with the use of dentures). Normal and immunocompromised patients can be treated.

3. Tinea pedis, tinea corporis, tinea cruris, tinea versicolor and dermal Candida infections.

4. Systemic candidiasis including candidaemia, disseminated candidiasis and other forms of invasive candidal infections. These include infections of the peritoneum, endocardium, pulmonary and urinary tract. Candidal infection in patients with malignancy, in intensive care units or those receiving cytotoxic or immunosuppressive therapy may be treated.

5. Cryptococcosis, including cryptococcal meningitis and infections of other sites (e.g. pulmonary, cutaneous). Normal hosts may be treated, as may patients with AIDS, organ-transplants or other causes of immunosuppression. Fluconazole may be used as maintenance treatment, to prevent relapses of cryptococcal disease in patients with AIDS.

6. For the prevention of fungal infections in immunocompromised patients who are considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, including bone marrow transplant.
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 greater than 90%. Oral absorption is not affected by simultaneous food intake. Maximum fasting plasma concentrations are reached 0.5-1.5h after administration of the dose. The plasma concentration is proportional to the dose. 90% of the steady-state level is reached 4-5 days after dosing once daily.

Fluconazole achieves good penetration into all body fluids studied. The fluconazole concentrations in saliva and sputum are comparable to the plasma concentrations. Fluconazole is broken down to a modest extent. Fluconazole is mainly excreted via the kidneys. Approximately 80% of the dose is excreted in non-metabolized form in the urine. Fluconazole clearance is proportional to the creatinine clearance. There is no evidence of circulating metabolites.

The medicinal product is presented as a clear, colourless solution for infusion. In the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products. This medicine is not for self-administration; it will be administered to the patient by a healthcare professional.

No new preclinical or clinical studies were conducted, which is acceptable given that this is a generic application cross-referring to a product that has been licensed for over 10 years. Bioequivalence studies are not necessary to support this application for a parenteral product.

The MHRA considers that the pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation holder (MAH) has provided adequate justification for not submitting a Risk Management Plan (RMP) and Environmental Risk Assessment (ERA). The lack of an Environmental Risk Assessment is justified since the application is for a generic version of an approved product and it is not likely to change the total market of fluconazole.
ACTIVE SUBSTANCE

Fluconazole

Nomenclature:

INN: Fluconazole
Chemical names: 2,4-Difluoro-α,α-bis(1H-1,2,4-triazol-1-ylmethyl) benzylalcohol
α-(2,4-Difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-1H-1,2,4-triazol-1-ethanol
2-(2,4-difluorophenyl)-1,3-bis-(1H-1,2,4-triazol-1-yl)-2-propanol

Structure:

Molecular formula: C_{13}H_{12}F_{2}N_{6}O
Molecular weight: 306.27 g/mol
CAS No: 86386-73-4
Physical form: A white hygroscopic crystalline powder
Solubility: Slightly soluble in water, freely soluble in methanol and soluble in acetone. It shows polymorphism

The active substance, fluconazole, is the subject of a European Pharmacopoeia (Ph. Eur.) monograph.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

An appropriate active substance specification has been provided, as set by the active substance manufacturer (ASMF). Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided for three batches and comply with the proposed specifications. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.
The active substance is stored in appropriate packaging. It is packed into inner and outer low density polyethylene (LDPE) bags, with silica gel between the two bags which are sealed with plastic closures. The packed, sealed bags are placed in polyethylene drums. Specifications and Certificates of Analysis for all packaging components used have been provided. The polyethylene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and also comply with Ph. Eur. 3.1.3 Polyolefines.

Appropriate stability data have been generated for active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and support a retest period of 5 years, with no specific storage conditions.
MEDICINAL PRODUCT

Description & Composition
The medicinal product is presented in polyvinyl chloride (PVC) infusion bags as a clear, colourless solution for infusion.

Other ingredients consist of pharmaceutical excipients, namely sodium chloride (for pH adjustment) and water for injections. Appropriate justification for the inclusion of each excipient has been provided. All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product.

There were no novel excipients used and no overages.

No overages are included in the composition of the product. However the filling volumes are adjusted to 51.2 mL, 102.2 mL & 201.7 mL for the 50, 100 and 200 mL pack sizes respectively in order to comply with extractable volume. This is acceptable.

Pharmaceutical development
Details of the pharmaceutical development of the drug product have been supplied and are satisfactory.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Satisfactory validation data were provided for three pilot scale batches of each presentation. All data were within specification.

Finished product specification
The finished product specifications are provided for both release and shelf life and are acceptable, they provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory Certificates of Analysis have been provided for three pilot scale batches of each of the product presentations. All parameters are within specification and comparable. Certificates of Analysis have been provided for any reference standards used.

Container Closure System
The medicinal product is presented in polyvinyl chloride (PVC) infusion bags with polycarbonate stoppers containing 50ml, 100ml or 200ml solution. The PVC bags are contained in polyester/ aluminium/ polypropylene overbags which are packaged, with
the product information leaflet, in cardboard outer cartons. Each carton contains 5 or 10 bags, although the MAH has stated that not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all packaging components used have been provided, and are satisfactory. All primary packaging satisfies Directive 2002/72/EC (as amended), and is suitable for contact with parenteral preparations.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 24 months has been set, with storage instructions ‘Do not refrigerate or freeze.’. This is satisfactory.

Leachables and extractables were studied and data have been provided for three laboratory pilot batches. The levels found in the product are well below toxicological levels.

**Bioequivalence Study**
A bioequivalence study is not necessary to support this application for a parenteral product. The MAH has presented data on a comparative study performed between their product and the reference product to demonstrate they have a product of equivalent quality.

**EXPERT REPORT**
A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**PRODUCT INFORMATION:**
The approved SmPC, leaflet, and labelling are satisfactory. Colour mock-ups of the labelling and PIL have been provided.

**Conclusion**
The proposed product, Fluconazole 2mg/ml Solution for Infusion, has been shown to be a generic version of the reference product, Diflucan Intravenous Infusion 2mg / ml (PL 00057/0315, Pfizer Ltd), with respect to qualitative and quantitative content of the active substance, and the pharmaceutical form. The test product is pharmaceutically equivalent to the reference product, which has been licensed in the UK for over 10 years. Given the route of administration and pharmaceutical form, it is not necessary to demonstrate bioequivalence of the proposed product to the reference product.

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. A Marketing Authorisation has therefore been granted.
NON-CLINICAL ASSESSMENT

The application was submitted as a national, abridged, application, according to Article 10.1 of Directive 2001/83/EC, as amended.

Leachables and extractables of the container closure system were studied and data have been provided for three laboratory pilot batches. The levels found in the product are well below toxicological levels.

A non-clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the expert has been supplied.
INDICATIONS
Fluconazole 2mg/ml Solution for Infusion is indicated in the following:

1. Genital candidiasis. Vaginal candidiasis, acute or recurrent. Candidal balantis. The treatment of partners who present with symptomatic genital candidiasis should be considered.

2. Mucosal candidiasis. These include oropharyngeal, oesophageal non-invasive bronchopulmonary infections, candiduria, mucocutaneous and chronic oral atrophic candidiasis (associated with the use of dentures). Normal and immunocompromised patients can be treated.

3. Tinea pedis, tinea corporis, tinea cruris, tinea versicolor and dermal *Candida* infections.

4. Systemic candidiasis including candidaemia, disseminated candidiasis and other forms of invasive candidal infections. These include infections of the peritoneum, endocardium, pulmonary and urinary tract. Candidal infection in patients with malignancy, in intensive care units or those receiving cytotoxic or immunosuppressive therapy may be treated.

5. Cryptococcosis, including cryptococcal meningitis and infections of other sites (e.g. pulmonary, cutaneous). Normal hosts may be treated, as may patients with AIDS, organ-transplants or other causes of immunosuppression. Fluconazole may be used as maintenance treatment, to prevent relapses of cryptococcal disease in patients with AIDS.

6. For the prevention of fungal infections in immunocompromised patients who are considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, including bone marrow transplant.

The indications are consistent with those of the reference product and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION
Full details concerning the posology are provided in the SmPC. The posology is consistent with that for the reference product and is satisfactory.

TOXICOLOGY
No new data have been submitted and none are required for this type of application.

CLINICAL PHARMACOLOGY
The clinical pharmacology of fluconazole is well known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for this application.

Pharmacodynamics
Fluconazole belongs to the triazole class of antimycotics (ATC Code J02A C01). It is a potent and selective inhibitor of fungal enzymes necessary for the synthesis of ergosterol. Fluconazole is very specific for fungal cytochrome P450 dependent enzymes.
Pharmacokinetics

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 greater than 90%. Oral absorption is not affected by simultaneous food intake. Maximum fasting plasma concentrations are reached 0.5-1.5h after administration of the dose. 90% of the steady-state level is reached 4-5 days after dosing once daily.

Fluconazole achieves good penetration into all body fluids studied. Fluconazole is mainly excreted via the kidneys. Approximately 80% of the dose is excreted in non-metabolized form in the urine. Fluconazole clearance is proportional to the creatinine clearance. There is no evidence of circulating metabolites.

Efficacy

No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical overview. The efficacy of fluconazole is well-established from its extensive use in clinical practice.

Fluconazole 2mg/ml Solution for Infusion is to be administered as an aqueous intravenous solution and contains the same active substance, in the same concentration, as the UK reference product Diflucan Intravenous Infusion 2mg / ml (Pfizer Ltd). Thus, in accordance with the “Note for Guidance on the Investigation of Bioavailability and Bioequivalence”, (CPMP/EWP/QWP/1401/98), the applicant is not required to submit a bioequivalence study.

Safety

No new data are submitted and none are required for this type of application. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of fluconazole is well-known.

Expert Report

The clinical overview contains a sufficient outline of the published literature concerning the clinical pharmacology, efficacy and safety of fluconazole. The report was prepared by an appropriately qualified expert for whom a satisfactory CV has been supplied.

Product Information:

Summary of Product Characteristics (SmPC)

The approved SmPC is consistent with that for the reference product and is acceptable.

Patient Information Leaflet (PIL)

The final PIL is in line with the approved SmPC and is satisfactory.

Labelling

The labelling is satisfactory.
CONCLUSION
The grounds for establishing the proposed product, Fluconazole 2mg/ml Solution for Infusion, as a generic version of the reference product, Diflucan Intravenous Infusion 2mg / ml (PL 00057/0315), are considered adequate. The product literature is approved.

Sufficient clinical information has been submitted to support this application. When used as indicated, Fluconazole 2mg/ml Solution for Infusion has a favourable benefit-to-risk ratio. The grant of a Marketing Authorisation was recommended on clinical grounds.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Fluconazole 2mg/ml Solution for Infusion are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
Leachables and extractables of the container closure system were studied and data have been provided for three laboratory pilot batches. The levels found in the product are well below toxicological levels.

EFFICACY
The applicant’s Fluconazole 2mg/ml Solution for Infusion has been demonstrated to be a generic version of the reference product, Diflucan Intravenous Infusion 2mg / ml (PL 00057/0315, Pfizer Ltd).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The approved SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The testing shows that patients/users are able to act upon the information that the leaflet contains.

Colour mock-ups of the labelling have been provided. The approved labelling artwork complies with statutory requirements.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s Fluconazole 2mg/ml Solution for Infusion and the reference product, Diflucan Intravenous Infusion 2mg / ml (Pfizer Ltd), are interchangeable. Extensive clinical experience with fluconazole is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit ratio is considered to be positive.
Fluconazole 2 mg/ml solution for infusion

(fluconazole)

PL 24780/0003

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the marketing authorisation application on 2nd February 2007
2. Following standard checks and communication with the applicant the MHRA considered the applications valid on 21st March 2007
3. Following assessment of the applications the MHRA requested further information relating to the quality dossier on 20th June 2008 and 29th June 2009
4. The applicant responded to the MHRA’s requests, providing further information for the quality sections on 30th October 2008 and 14th September 2009 respectively
5. The application was determined on 22nd February 2010
Fluconazole 2 mg/ml solution for infusion

(fluconazole)

PL 24780/0003

STEPS TAKEN AFTER AUTHORIZATION-SUMMARY

The following table lists non-safety updates to the Marketing Authorisation for this product that have been approved by the MHRA since the product was first licensed. The update has been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/02/2012</td>
<td>Type 1B</td>
<td>To update sections 2, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC and Patient Information Leaflet (PIL) in line with the Article 30 Decision for Diflucan (dated 02/09/2011).</td>
<td>Granted 28/05/2012</td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Fluconazole 2mg/ml Solution for Infusion is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Fluconazole 2mg/ml Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of solution for infusion contains 2mg fluconazole.

Each 50 ml infusion bag contains 100mg fluconazole.
Each 100 ml infusion bag contains 200mg fluconazole.
Each 200 ml infusion bag contains 400mg fluconazole.
Also contains 15 mmol sodium per 100 ml dose.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Solution for Infusion
Infusion bag containing a clear, colourless solution.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Therapy may be initiated before the results of cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

Fluconazole is indicated in the treatment of the following conditions:

1. Genital candidiasis. Vaginal candidiasis, acute or recurrent. Candidal balantis. The treatment of partners who present with symptomatic genital candidiasis should be considered.

2. Mucosal candidiasis. These include oropharyngeal, oesophageal non-invasive bronchopulmonary infections, candiduria, mucocutaneous and chronic oral atrophic candidiasis (associated with the use of dentures). Normal and immunocompromised patients can be treated.

3. Tinea pedis, tinea corporis, tinea cruris, tinea versicolor and dermal Candida infections.

4. Systemic candidiasis including candidaemia, disseminated candidiasis and other forms of invasive candidal infections. These include infections of the peritoneum, endocardium, pulmonary and urinary tract. Candidal infection in patients with malignancy, in intensive care units or those receiving cytotoxic or immunosuppressive therapy may be treated.

5. Cryptococcosis, including cryptococcal meningitis and infections of other sites (e.g. pulmonary, cutaneous). Normal hosts may be treated, as may patients with AIDS, organ-transplants or other causes of immunosuppression. Fluconazole may be used as maintenance treatment, to prevent relapses of cryptococcal disease in patients with AIDS.

6. For the prevention of fungal infections in immunocompromised patients who are considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, including bone marrow transplant.
4.2 Posology and method of administration

Fluconazole should be administered by intravenous infusion at a rate of approximately 5-10ml/min. On transferring from the intravenous route to the oral route or vice versa, there is no need to change the daily dose.

The daily dose of fluconazole should be based on the nature and severity of the fungal infection. Most cases of vaginal candidiasis respond to single dose therapy. Therapy for those types of infections which require multiple dose treatment should be continued until clinical parameters or laboratory tests indicate that active fungal infection has subsided. An inadequate period of treatment may lead to the recurrence of active infection. Patients with AIDS and cryptococcal meningitis usually require maintenance therapy to prevent relapse.

Adults

1. Candidal vaginitis or balantis – 150mg single oral dose.
2. Mucosal candidiasis
   Oropharyngeal candidiasis - the usual dose is 50 mg once daily for 7 - 14 days. Treatment should not normally exceed 14 days except in severely immunocompromised patients.
   Atrophic oral candidiasis associated with dentures – the usual dose is 50 mg once daily for 14 days, administered concurrently with local antiseptic measures to the denture.
   For other candidal infections of the mucosa except genital candidiasis e.g. oesophagitis, non-invasive bronchopulmonary infections, candiduria, mucocutaneous candidiasis etc., the usual effective dose is 50 mg daily, given for 14 - 30 days.
   In unusually difficult cases of mucosal candidal infections, the dose may be increased to 100 mg daily.
3. For tinea pedis, corporis, cruris, versicolor and dermal Candida infections, the recommended dosage is 50 mg once daily. Duration of treatment is normally 2 to 4 weeks but tinea pedis may require treatment for up to 6 weeks. Duration of treatment should not exceed 6 weeks.
4. For candidaemia, disseminated candidiasis and other invasive candidal infections, the usual dose is 400 mg on the first day, followed by 200 mg daily. Depending on the clinical response, the dose may be increased to 400 mg daily. Duration of treatment is based upon the clinical response.
5. Cryptococcal infection
   For cryptococcal meningitis and cryptococcal infections at other sites, the usual dose is 400 mg on the first day, followed by 200 - 400 mg once daily. The duration of treatment for cryptococcal infections will depend upon the clinical and mycological response but is usually at least 6 - 8 weeks for cryptococcal meningitis.
   For the prevention of relapse of cryptococcal meningitis in patients with AIDS, after the patient receives a full course of primary therapy, fluconazole may be administered indefinitely at a daily dose of 100 - 200 mg.
6. For the prevention of fungal infections in immunocompromised patients who are considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, the dose should be 50 - 400 mg once daily, based on the patient's risk for developing fungal infection. For patients at high risk of systemic infection, e.g. patients who are anticipated to have profound or prolonged neutropenia such as during bone marrow transplantation, the recommended dose is 400 mg once daily. Fluconazole administration should start several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 1,000 cells per mm3.

Children

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.

Children over four weeks of age

The recommended dose of fluconazole for mucosal candidiasis is 3 mg/kg daily. A loading dose of 6 mg/kg may be used on the first day, to achieve steady state levels more rapidly.

For the treatment of systemic candidiasis and cryptococcal infection, the recommended dosage is 6 - 12 mg/kg daily, depending on the severity of the disease.
For the prevention of fungal infections in immunocompromised patients, who are considered at risk as a consequence of neutropenia, following cytotoxic chemotherapy or radiotherapy, the dose should be 3 - 12 mg/kg daily, depending on the extent and duration of the induced neutropenia (see adult dosing).

A maximum dosage of 400 mg daily should not be exceeded in children.

Despite extensive data supporting the use of fluconazole in children, there are limited data available on the use of fluconazole for genital candidiasis in children below 16 years. Use at present is not recommended unless antifungal treatment is imperative and no suitable alternative agent exists.

Children four weeks of age and younger
Neonates excrete fluconazole slowly. In the first two weeks of life, the same mg/kg dosing used in older children should be adopted but administered every 72 hours. During weeks 3-4 of life, the same dose should be given every 48 hours.

A maximum dosage of 12 mg/kg every 72 hours should not be exceeded in children in the first two weeks of life. For children between three and four weeks of life, 12 mg/kg every 48 hours should not be exceeded.

Elderly
The normal adult dose should be used if there is no evidence of renal impairment. In patients with renal impairment (creatinine clearance less than 50 ml/min), the dosage schedule should be adjusted as described below.

Patients with renal impairment
Fluconazole is excreted predominantly in the urine as unchanged drug. No adjustments in single dose therapy are required for those with renal impairment. In patients (including children) with impaired renal function who will receive multiple doses of fluconazole, the normal recommended dose (according to indication) should be given on day 1, followed by a daily dose based on the following table:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Percent of recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>100 %</td>
</tr>
<tr>
<td>11 - 50</td>
<td>50 %</td>
</tr>
<tr>
<td>Patients receiving regular dialysis</td>
<td>100% after each dialysis session</td>
</tr>
</tbody>
</table>

4.3 Contraindications
Fluconazole should not be used in patients with known hypersensitivity to fluconazole or to related azole compounds or any of the excipients.

Co-administration of terfenadine or cisapride is contraindicated in patients receiving fluconazole. (See section 4.5).

4.4 Special warnings and precautions for use
In some patients, particularly those with serious underlying diseases such as AIDS and cancer, abnormalities in haematological, hepatic, renal and other biochemical function test results have been observed during treatment with fluconazole. However, the clinical significance and relationship to treatment is uncertain.

Very rarely, patients who died with severe underlying disease and who had received multiple doses of fluconazole, had post-mortem findings which included hepatic necrosis. These patients were receiving multiple concomitant medications, some known to be potentially hepatotoxic and/or had underlying diseases which could have caused the hepatic necrosis.

In cases of hepatotoxicity, no obvious relationship to the total daily dose of fluconazole, the duration of therapy or the sex or age of the patient has been observed. The abnormalities have usually been reversible on discontinuation of fluconazole therapy.
As a causal relationship with fluconazole cannot be excluded, patients who develop abnormal liver function tests during fluconazole therapy should be monitored for the development of more serious hepatic injury. Fluconazole should be discontinued, if clinical signs or symptoms consistent with liver disease develop during treatment.

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 drugs.

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

In rare cases, as with other azoles, anaphylaxis has been reported.

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 torsade de points in patients taking fluconazole. Although the association of fluconazole and QT-prolongation has not been fully established, fluconazole should be used with caution in patients with potentially proarrythmic conditions such as:
- Congenital or documented acquired QT prolongation
- Cardiomyopathy, in particular when heart failure is present
- Sinus bradycardia
- Existing symptomatic arrythmias
- Concomitant medication not metabolized by CY34A but known to prolong QT interval
- Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalaemia

Fluconazole Solution for Infusion is formulated in a 0.9% sodium chloride solution, with each 100 mg (50 ml bag) containing 7.5 mmol each of Na⁺ and Cl⁻, each 200 mg (100 ml bag) containing 15 mmol each of Na⁺ and Cl⁻ and each 400 mg (200 ml bag) containing 30 mmol each of Na⁺ and Cl⁻. This should be considered in patients on a sodium or fluid restricted diet.

4.5 Interaction with other medicinal products and other forms of interaction

The following drug interactions relate to the use of multiple-dose fluconazole; their relevance to single-dose fluconazole has not yet been established.

**Anticoagulants:** In an interaction study, fluconazole increased the prothrombin time (12 %) after warfarin administration in healthy males. In post-marketing experience, as with otherazole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria and melaena) have been reported in association with increases in prothrombin time, in patients receiving fluconazole concurrently with warfarin. Prothrombin time in patients receiving coumarin-type anticoagulants should be carefully monitored.

**Benzodiazepines (short acting):** Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. This effect on midazolam appears to be more pronounced following oral administration of fluconazole, than with fluconazole administered intravenously. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dosage and the patients should be appropriately monitored.

**Endogenous steroids:** Fluconazole 50 mg daily does not affect endogenous steroid levels in females: 200 - 400 mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers.

**Sulphonylureas:** Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulphonylureas (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Fluconazole and oral sulphonylureas may be given jointly to diabetic patients, although the possibility of a hypoglycaemic episode must be considered. Blood glucose levels must therefore be monitored and the dose of sulphonylurea adjusted accordingly.
**Hydrochlorothiazide:** In a pharmacokinetic interaction study, the co-administration of multiple doses of hydrochlorothiazide in healthy volunteers receiving fluconazole, increased the plasma concentrations of fluconazole by 40%. An effect of this magnitude should not require any change in the dosage regimen of fluconazole in patients simultaneously receiving diuretics, although this should be taken into consideration by the prescriber.

**Phenytoin:** The concomitant administration of fluconazole and phenytoin may increase levels of phenytoin to a clinically significant degree. If both drugs need to be given concomitantly, levels of phenytoin must be monitored and the dose of phenytoin adjusted to maintain therapeutic levels.

**Oral contraceptives:** Two pharmacokinetic studies were conducted with combined oral contraceptives and multiple fluconazole doses. In the study using 50 mg fluconazole, there were no relevant effects on hormone level. However, using 200 mg fluconazole daily, the area under the curve (AUC) for ethinylestradiol and levonorgestrel, increased by 40% and 24% respectively. Thus, multiple dose use of fluconazole at these levels is unlikely to affect the efficacy of combined oral contraceptives.

In a 300mg once weekly fluconazole study, the AUCs of ethinyl oestradiol and norethindrone were increased by 24% and 13% respectively.

**Rifampicin:** The concomitant administration of fluconazole and rifampicin gave rise to a 25% reduction in the AUC and a 20% shorter half-life of fluconazole. Thus, an increase in the dose of fluconazole should be considered for patients receiving concomitant rifampicin.

**Ciclosporin:** A pharmacokinetic study conducted on kidney transplant patients showed that a daily dose of 200 mg fluconazole slowly increased the concentrations of ciclosporin. However, another multiple-dose study using 100 mg fluconazole daily showed that levels of ciclosporin were not affected in patients following bone marrow transplants. Thus, the monitoring of the plasma concentration of ciclosporin is recommended in patients taking fluconazole.

**Theophylline:** In a placebo-controlled interaction study, the administration of 200 mg fluconazole daily for 14 days, led to a reduction of 18% in the mean plasma clearance figure of theophylline. Therefore, patients receiving high doses of theophylline or patients with high risk of theophylline toxicity, should be carefully monitored for signs of theophylline toxicity when receiving fluconazole. Treatment should be appropriately modified if signs of toxicity develop.

**Terfenadine:** Due to the occurrence of serious dysrhythmias (secondary to prolongation of the QTc interval), in patients receiving other azole antifungals in conjunction with terfenadine, interaction studies have been performed. In one study, a 200 mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. In another study, a 400 mg and 800 mg daily dose of fluconazole demonstrated that fluconazole, taken in multiple doses of 400 mg per day or greater, significantly increased plasma levels of terfenadine when taken concomitantly. There have been spontaneously reported cases of palpitations, tachycardia, dizziness and chest pain in patients taking concomitant fluconazole and terfenadine, where the relationship of the reported adverse events to drug therapy or underlying medical conditions was not clear. Because of the potential seriousness of such an interaction, it is recommended that terfenadine should not be taken in combination with fluconazole. (See section 4.3).

**Cisapride:** There have been reports of cardiac events including torsades de pointes, in patients to whom fluconazole and cisapride were co-administered. 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 QTc interval. In most of these cases, the patients appear to have been predisposed to arrhythmias or had serious underlying illnesses and the relationship of the reported events to a possible fluconazole-cisapride drug interaction is unclear. Because of the potential seriousness of such an interaction, it is recommended that cisapride is not taken in combination with fluconazole. (See section 4.3, ‘Contra-indications’.)

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**UKPAR Fluconazole 2 mg/ml Solution for Infusion**

**PL 24780/0003**
**Zidovudine:** Two pharmacokinetic studies have shown increases in levels of zidovudine most likely caused by the decreased conversion of zidovudine to its main metabolite. One study determined the levels of zidovudine in AIDS or ARC patients before and after the daily administration of 200 mg fluconazole for 15 days. A significant increase was observed in the zidovudine AUC (20%). A second randomised two-period, two-treatment crossover study, examined the levels of zidovudine in patients infected with HIV. On two occasions, with an interval of 21 days, patients received 200 mg zidovudine every 8 hours, either with or without 400 mg of fluconazole daily, for 7 days. The AUC of zidovudine increased significantly (74%) during co-administration with fluconazole. Therefore, patients receiving this combination should be monitored for the appearance of adverse reactions related to zidovudine.

**Rifabutin:** There have been reports that an interaction exists when fluconazole is administered concomitantly with rifabutin, leading to increased serum levels of rifabutin. There have also been reports of uveitis in patients to whom fluconazole and rifabutin were co-administered. Patients receiving rifabutin and fluconazole concomitantly should be carefully monitored.

**Tacrolimus:** There have been reports that an interaction exists when fluconazole is administered concomitantly with tacrolimus, leading to increased serum levels of tacrolimus. There have also been reports of nephrotoxicity in patients to whom fluconazole and tacrolimus were co-administered. Patients receiving tacrolimus and fluconazole concomitantly should be carefully monitored.

The use of fluconazole in patients concurrently taking astemizole or other drugs metabolised by the cytochrome P450 system, may be associated with elevations in serum levels of these drugs. In the absence of definitive information, caution should be used when co-administering fluconazole. This is particularly important for drugs known to prolong the QT interval. Patients should be carefully monitored.

While no interaction studies have been conducted with other drugs, the possible appearance of other pharmacological interactions is not ruled out.

### 4.6 Pregnancy and lactation

**Pregnancy:**
There are no adequate and well-controlled studies in pregnant women. There have been reports of multiple congenital abnormalities, in infants whose mothers were being treated for three or more months with high dose (400 - 800 mg/day) fluconazole therapy for coccidioidomycosis. The relationship between fluconazole and these events is unclear. Adverse events on reproduction in animal studies have been reported (see section 5.3). Accordingly, use in pregnancy should be avoided, except in patients with severe or potentially life-threatening fungal infections, in whom fluconazole may be used if the anticipated benefit outweighs the possible risk to the foetus. Fluconazole should not be used in women of childbearing potential, unless adequate contraception is employed.

**Lactation:**
Fluconazole is found in human breast milk at concentrations similar to plasma, hence its use in nursing mothers is not recommended.

### 4.7 Effects on ability to drive and use machines

Experience with fluconazole indicates that therapy is unlikely to affect a patient's ability to drive or use machinery.

### 4.8 Undesirable effects

Fluconazole is generally well tolerated.

The most common side effects observed during clinical trials and associated with fluconazole are:

**Nervous system disorders:**
Headache
**Gastrointestinal disorders:**
Abdominal pain, diarrhoea, flatulence, nausea.
In some patients, particularly those with serious underlying diseases such as AIDS and cancer, changes in renal and hematological function test results and hepatic abnormalities have been observed during treatment with fluconazole and comparative agents but the clinical significance and relationship to treatment is uncertain, (see section 4.4).

**Hepatobiliary disorders:**
Hepatic toxicity including rare cases of fatality, elevated alkaline phosphatase, elevated bilirubin, elevated SGOT, elevated SGPT.

**Skin and subcutaneous tissue disorders:**
Rash.

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

**Blood and lymphatic system disorders:**
Leukopenia (including neutropenia and agranulocytosis), thrombocytopenia.

**Immune system disorders:**
Allergic reaction: Anaphylaxis (including angioedema, face oedema, pruritus), urticaria.

**Metabolism and nutrition disorders:**
Hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia.

**Nervous system disorders:**
Dizziness, seizures, taste perversion.

**Gastrointestinal disorders:**
Dyspepsia, vomiting.

**Hepatobiliary disorders:**
Hepatic failure, hepatitis, hepatocellular necrosis, jaundice.

**Skin and subcutaneous tissue disorders:**
Alopecia, exfoliative skin disorders, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

**Cardiac disorders:**
QT prolongation, torsade de pointes

### 4.9 Overdose
There has been a reported case of overdose with fluconazole. A 42 year-old patient infected with human immunodeficiency virus, developed hallucinations and exhibited paranoid behaviour after reportedly ingesting 8200 mg fluconazole, unverified by his physician. The patient was admitted to hospital and his condition resolved within 48 hours.

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

As 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
ATC code: JO2AC01
Pharmacotherapeutic group: Antimycotic for systemic use
Fluconazole, a member of the triazole class of antifungal agents, is a potent and selective inhibitor of fungal enzymes necessary for the synthesis of ergosterol.

Fluconazole shows little pharmacological activity in a wide range of animal studies. Some prolongation of pentobarbitone sleeping times in mice (p.o.), increased mean arterial and left ventricular blood pressure and increased heart rate in anaesthetised cats (i.v.) occurred. Inhibition of rat ovarian aromatase was observed at high concentrations.

Fluconazole is highly specific for fungal cytochrome P-450 dependent enzymes.

Fluconazole 50 mg daily, when given for up to 28 days, has been shown not to affect testosterone plasma concentrations in males or steroid concentrations in females of child-bearing age. Fluconazole 200 - 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.

There have been reports of cases 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.

5.2 Pharmacokinetic properties

Fluconazole's pharmacokinetic properties are similar following its oral or intravenous administration. Orally administered fluconazole is well absorbed, with plasma levels (and systemic bioavailability) being over 90% of the levels achieved following intravenous administration. Absorption by the oral route is not affected by the joint administration of food. Maximum plasma concentrations when fasting are obtained between 0.5 and 1.5 hours post-dose, with a clearance half-life of approximately 30 hours.

Plasma concentrations are proportional to the dose. 90% steady state levels are reached after 4 or 5 days with multiple once daily doses. The administration of a higher dose on the first day, double that of the normal daily dose, raises plasma levels to 90% of the equilibrium status levels by the second day.

The apparent volume of distribution is close to that of total body water. 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. High skin concentrations of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. Binding to plasma proteins is low (11 - 12%).

Clearance is mostly renal, with approximately 80% of the unmodified dose appearing in the urine. The clearance of fluconazole is proportional to creatinine clearance. There is no evidence of circulating metabolites.

Fluconazole's long plasma elimination half-life, makes it possible to administer a single dose in the treatment of genital candidiasis and a daily dose in the treatment of other indications.

5.3 Preclinical safety data

Preclinical data from conventional studies on repeat dose toxicity, genotoxicity or carcinogeticity indicate no special hazard for humans.

In reproduction toxicity studies in rat, an increased incidence of hydronephrosis and extension of renal pelvis was reported at 25 mg/kg. An increase in embryonal lethality, anatomical variations and delayed ossification was noted at doses ranging from 80 mg/kg to 300 mg/kg (approximately 12- to 45-fold the maximum recommended human dose. Prolonged delivery and dystocia have been observed at 20mg/kg. These effects are consistent with the inhibition
of oestrogen synthesis in rats and may be a result of known effects of lowered oestrogen on pregnancy, organogenesis and parturition.

In reproduction studies in rabbits, abortions were recorded.

Adverse effects on reproduction in human have been reported (see section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium chloride
Water for injections

6.2 Incompatibilities
In the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Do not refrigerate or freeze.

6.5 Nature and contents of container
Polyvinyl chloride (PVC) infusion bag with polycarbonate stopper containing 50ml, 100ml and 200ml solution. The PVC bags are contained in a polyester/ aluminium/ polypropylene overbag. Each carton contains 5 or 10 bags. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
For single use only. Discard any remaining solution. Fluconazole Solution for Infusion should be infused at a rate of no more than 10 ml/min.

7 MARKETING AUTHORISATION HOLDER
Villerton Invest S.A.
8-10, Rue Jean Monnet,
L-2180 Luxembourg

8 MARKETING AUTHORISATION NUMBER(S)
PL 24780/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/02/2010

10 DATE OF REVISION OF THE TEXT
22/02/2010
UKPAR Fluconazole 2 mg/ml Solution for Infusion

PL 24780/0003

PRODUCT INFORMATION LEAFLET

Fluconazole 2 mg/ml Solution for Infusion

Read all of this leaflet carefully before you start using this medicine.

Keep this leaflet. You may need to read it again.

If you have any further questions, ask your doctor or nurse.

This medicine has been prescribed for you. Do NOT pass it on to others. It may harm them even if their symptoms are the same as yours.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

In this leaflet:
1. What Fluconazole is and what it is used for
2. Before you are given Fluconazole Infusion
3. How Fluconazole Infusion is given
4. Possible side effects
5. How to store Fluconazole Infusion
6. Further information

1. WHAT FLUCONAZOLE IS AND WHAT IT IS USED FOR

Your medicine contains the active substance fluconazole, which is one of a group of medicines called antifungal agents.

Fluconazole is used to treat infections caused by fungi or yeasts.

It may also be used to prevent you from getting a fungal infection.

You may be given Fluconazole by your doctor to treat fungal infections such as:
- thrush of the mouth or throat (mucosal infections), thrush is commonly caused by Candida;
- internal (systemic) fungal infections caused by Candida, e.g. infections in the throat, urinary tract or other body organs;
- fungal or yeast infections caused by Cryptococcus e.g. cryptococcal meningitis, and infections in other organs such as the lungs;
- fungal infections of the skin e.g. dermatomycosis;
- genital Candida infections e.g. vaginal thrush or Candida infections of the mouth (thrush) in infants (information at the end of the package leaflet).

You may also be given this medicine to:
- keep you from getting a fungal infection if your immune system is not working properly;
- stop an infection caused by Cryptococcus from coming back (in AIDS patients).

2. BEFORE YOU ARE GIVEN FLUCONAZOLE INFUSION

You should not be given Fluconazole:
- if you are allergic (hypersensitive) to Fluconazole;
- if you are allergic to any of the other ingredients of this medicine (see section 6. Further Information).

If you have ever had an allergic reaction to any other medicines used to treat a fungal infection, this may have caused lesions or swelling of the skin or difficulty in breathing.

If you are taking terfenadine or astemizole (used for stomach upset), ask your doctor if you are taking terfenadine or astemizole.

Take special care with Fluconazole Infusion and tell your doctor or nurse:
- if you have liver or kidney problems;
- if you are pregnant or breast feeding (see "Pregnancy and breast-feeding");
- if you are on a low sodium diet or if you are restricting the amount of fluids you are taking (see "Important information about some of the ingredients of Fluconazole Infusion");
- if your symptoms do not improve or if they are getting worse;
- if you suffer from heart disease including heart rhythm problems.

3. POSSIBLE SIDE EFFECTS

Taking other medicines:
Please tell your doctor if you are taking any of the following medicines:
- fexofenadine, especially if you have liver problems;
- certain medicines for diabetes, like sulphonylureas, such as chlorpropamide, glibenclamide, tolbutamide and repaglinide;
- propranolol (for high blood pressure and fluid retention);
- phenytin or spironolactone;
- ciclosporin or tacrolimus (not used to affect the immune system);
- Clopidogrel (antiplatelet agent);
- trimethoprim or thiazides (information at the end of the package leaflet);
- clofibrate or fenofibrate (used in high cholesterol patients);
- oral contraceptives;
- statins or certain drugs to control blood fats.

Please tell your doctor or pharmacist if you are taking or have recently taken, any other medicines including medicines obtained without a prescription.

Pregnancy and breast-feeding:
Tell the doctor or pharmacist if you are pregnant, if you might be pregnant or if you are breast-feeding before you are given this medicine.

Driving and using machines:
This medicine is likely to affect your ability to drive or use machines. However, some side effects may occur during the treatment e.g. dizziness; see section 4. "Possible Side Effects". If you feel dizzy, you should not drive or use machines.

Important information about some of the ingredients of Fluconazole Infusion is listed below:
- Do not use Fluconazole Infusion if you are allergic to them.
- If you are on a low sodium diet or if you are restricting the amount of fluids you are taking, see "Important information about some of the ingredients of Fluconazole Infusion".
- Some ingredients may affect the medicines you are taking, see "Important information about some of the ingredients of Fluconazole Infusion".
- If you have any side effects, tell your doctor or pharmacist, see "Possible Side Effects".

4. DIRECTIONS FOR USE

Take only as advised by your doctor or pharmacist.

In the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products.

Store in a cool, dry place.

Special precautions for handling and use of the device
Store the device in its original container. Do not refrigerate or freeze.

Preparation and method of administration
Fluconazole should be administered by intravenous infusion at a rate of approximately 1 mg/kg/min. It is prepared from the internal vial into the external vial to yield a 2 mg/ml saline infusion. There is no need to change the dosage. The daily dose of Fluconazole is based on the nature and severity of the fungal infection. Most cases of vaginal candidiasis respond to a single dose of therapy. Therapy for those patients who do not respond to a single dose should be continued until clinical parameters or laboratory tests indicate that active fungal infection has resolved. All cases of fungal infection should be treated for a minimum of 7 days. The use of this medicine may lead to the emergence of fluconazole-resistant fungi. Patients with AIDS and cryptococcal meningitis usually require maintenance therapy to prevent relapse.

Adults
1. Candida vaginitis or balanitis - 150 mg single dose.

2. Mycotic candidiasis - the usual dose is 50 mg once daily for 7 - 14 days. Treatment should normally exceed 14 days only in severely immunocompromised patients.

3. Cryptococcal meningitis - the recommended course is 50 mg once daily. Duration of treatment is normally 4 to 6 weeks but this period may require treatment for up to 4 weeks. Duration of treatment should not exceed 4 weeks.

4. For candidiasis, disseminated candidiasis and other invasive candidiasis, the usual dose is 300 mg once daily. Duration of treatment is normally 2 to 3 weeks. The use of this medicine may lead to the emergence of fluconazole-resistant fungi. Patients with AIDS and cryptococcal meningitis usually require maintenance therapy to prevent relapse.

5. Cryptococcal infection
For cryptococcal meningitis and cryptococcal infections at other sites, the usual dose is 500 mg once daily, given orally. Duration of treatment is normally 2 to 3 weeks. The use of this medicine may lead to the emergence of fluconazole-resistant fungi. Patients with AIDS and cryptococcal meningitis usually require maintenance therapy to prevent relapse.
UKPAR Fluconazole 2 mg/ml Solution for Infusion
PL 24780/0003

3. HOW FLUCONAZOLE INFUSION IS GIVEN

Your doctor or nurse will give you this medicine as an intravenous infusion ("drip") over a period of up to approximately 40 minutes.
Flucanazole infusion should not be mixed with any other medicines except infusion.

Your doctor will choose the daily dosage depending on your age and severity of the fungal infection. Your doctor may give you a higher dose and longer therapy depending on how you respond to treatment.

The Usual Dose of Fluconazole Infusion is as follows:

Adults, elderly and children over 12 years:
- Intravenous injections of the mouth: 50-100 mg once daily for 7-14 days.
- Intravenous injections of the mouth or as an oral dose: 100-500 mg once daily for 14-28 days.
- Intravenous fungi infections caused by Candida: 400 mg on the first day then 300-400 mg once daily.
- Intravenous fungi infections caused by Cryptococcus: 400 mg on the first day then 300-400 mg once daily for 2-4 weeks.
- Intravenous fungi infections caused by Candida: 150mg as a single dose.
- To stop fungal growth: Intravenous fungi infections: 40-50mg once daily until you are all clear of infection and have died or been infected.
- Intravenous fungi infections of the skin: 50-100 mg once daily.

Children up to 12 years old:
- Intravenous fungi infections of the mouth and throat: Smaller once daily or twice daily (a dose of 5mg/kg may be used on the first day)
- Intravenous fungi infections caused by Candida: 150mg once daily.
- Prevention of fungal infections: 3-12mg/kg once daily while at risk of getting an infection.

Children should not be given more than 400 mg/day.

The use of Fluconazole for treating candida infections in children under 16 years old is not recommended.

Newborns and Infants:
The usual dose in the same as that in older children but it should be administered as follows:
- 50 mg/kg once daily for babies aged 1-2 weeks.
- 25 mg/kg once daily for babies aged 2-4 weeks.

Patients with kidney problems:
If your kidneys are not working properly, you may need to give a different dose. Ask your doctor or nurse if you want to know what dose to give.

If you have been given more Fluconazole than you should:
This is unlikely to happen but tell your doctor or nurse immediately if you think you have been given too much Fluconazole.

4. POSSIBLE SIDE EFFECTS

Use all medicines, Fluconazole Infusion can cause side effects, although not everybody gets them.

A few people develop allergic reactions to medicines. If any of the following happen, tell your doctor immediately or go to the casualty department if you are your nearest hospital:
- itching rash, difficulty in breathing, tightness in chest
- swelling of eyes, face or lips
- rash, blistering of any other body part
- an rash all over your body

If you are an AIDS patient, you are more likely to get severe side effects to many drugs, including Fluconazole.

For the prevention of cryptococcal meningitis in patients with AIDS, after the patient receives a course of primary therapy, fluconazole may be administered indefinitely as a daily dose of 100-200 mg.

5. FURTHER INFORMATION

What Fluconazole Injection for infusion contains:
The active ingredient is Fluconazole 2mg/ml.
The other ingredients are sodium chloride and water for injections.

What Fluconazole Solution for infusion looks like and the contents of each pack:
You will receive a clear solution in a polyvinyl chloride (PVC) infusion bag, packed in a polyvinyl alcohol overwrap.
Each 50ml, 100ml and 200ml infusion bag contains 100mg, 200mg, and 400mg Fluconazole respectively.

Marketing Authorisation Holder:
Vifor Pharmaceutics, S.A., 1200 Geneva 20, Switzerland.

Manufacturer:
Apotheke v.d. Welt, CH-7749 Campogno, Switzerland.

This leaflet was last approved in February 2016.

LOGOFC209

LOGOFC209
LABELLING

Carton – 100mg in 50ml
UKPAR Fluconazole 2 mg/ml Solution for Infusion

Infusion bag label

Fluconazole 2mg/ml Solution for Infusion
100mg / 50ml
in 0.9% sodium chloride solution

Each ml solution for infusion contains 2mg
fluconazole. Also contains sodium chloride
and water for injections.
For I.V. infusion. For single use only.
Discard any unused solution.
Do not mix or co-administer with other
products or infusion solutions.
Use as directed by the physician.
Read package leaflet before use.
Keep out of the reach and sight of children.
Do not refrigerate or freeze,

PL 24780/0003
EAN 5060130130799
Villerton Invest SA
8-10 Rue Jean Monnet,
L2180-Luxembourg.

Batch: Exp.Date:

Overbag label

Fluconazole 2mg/ml Solution for Infusion
100mg / 50ml
in 0.9% sodium chloride solution

One single sterile unit PVC bag.
Each ml solution for infusion contains 2mg fluconazole.
Also contains sodium chloride and water for injections.
For I.V. infusion. For single use only. Discard any
unused solution. Do not mix or co-administer with
other products or infusion solutions. Use as directed
by the physician. See package leaflet before use.
Do not remove from outer foil until ready for use and use
promptly when outer is opened. Check for minute
leaks prior to use as, if found, sterility cannot be
guaranteed. Keep out of reach and sight of children.
Do not refrigerate or freeze.

PL 24780/0003
Villerton Invest SA
8-10, Rue Jean Monnet
L-2190 Luxembourg
Distributed by Bevertec Isbouque Limited
Chelk, Wrexham, LL14 5NE

Batch: Exp.Date:
Carton - 200mg in 100ml
Infusion bag label

Fluconazole 2mg/ml Solution for Infusion
200mg / 100ml
in 0.9% sodium chloride solution

Each ml solution for infusion contains 2mg fluconazole. Also contains sodium chloride and water for injections.
For I.V. infusion, For single use only, Discard any unused solution.
Do not mix or co-administer with other products or infusion solutions.
Use as directed by the physician.
Read package leaflet before use.
Keep out of the reach and sight of children.
Do not refrigerate or freeze.

PL 24780/0003
EAN 5069130130805
Villerton Invest SA
8-10 Rue Jean Monnet,
L2190-Luxembourg.

Overbag label

Fluconazole 2mg/ml Solution for Infusion
200mg / 100ml
in 0.9% sodium chloride solution

One single sterile unit PVC bag.
Each ml solution for infusion contains 2mg fluconazole. Also contains sodium chloride and water for injections.
For I.V. infusion, For single use only. Discard any unused solution. Do not mix or co-administer with other products or infusion solutions. Use as directed by the physician. See package leaflet before use. Do not remove from outer lot until ready for use and use promptly when outer is opened. Check for minute leaks prior to use as, if found, identity cannot be guaranteed. Keep out of reach and sight of children. Do not refrigerate or freeze.

PL 24780/0003
Villerton Invest SA
8-10 Rue Jean Monnet
L-2190 Luxembourg
Distributed by Bournemouth Ibisus Limited
Chink, Wrexham, LL14 2NS

Batch: Exp.Date:
Carton - 400mg in 200ml
Infusion bag label

Fluconazole 2mg/ml Solution for Infusion
400mg / 200ml in 0.9% sodium chloride solution

Each ml solution for infusion contains 2mg fluconazole. Also contains sodium chloride and water for injections. For I.V. infusion. For single use only. Discard any unused solution. Do not mix or co-administer with other products or infusion solutions. Use as directed by the physician. Read package leaflet before use. Keep out of the reach and sight of children. Do not refrigerate or freeze.

PL 24780/0003
EAN 5060130130812
Villerton Invest SA
8-10 Rue Jean Monnet,
L-2180-Luxembourg.

Fluconazole 400mg / 200ml

Batch: Exp.Date:

Overbag label

Fluconazole 2mg/ml Solution for Infusion
400mg / 200ml in 0.9% sodium chloride solution

One single sterile unit PVC bag. Each ml solution for infusion contains 2mg fluconazole. Also contains sodium chloride and water for injections.

For I.V. infusion. For single use only. Discard any unused solution. Do not mix or co-administer with other products or infusion solutions. Use as directed by the physician. See package leaflet before use. Do not remove from outer foil until ready for use and use promptly when outer is opened. Check for minute leaks prior to use as, if found, sterility cannot be guaranteed. Keep out of reach and sight of children. Do not refrigerate or freeze.

PL 24780/0003
Villerton Invest SA
8-10, Rue Jean Monnet
L-2180 Luxembourg
Distributed by Bowmed Ibisqua Limited
Chirk, Wrexham, LL14 5NS

Fluconazole 400mg / 200ml

Batch: Exp.Date:
Annex 1

Reference:  PL 24780/0003-0010

Product:  Fluconazole 2mg/ml Solution for Infusion

Marketing Authorisation Holder:  Villerton Invest SA

Active Ingredient(s):  Fluconazole

Reason
To update sections 2, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC and Patient Information Leaflet (PIL) in line with the Article 30 Decision for Diflucan (dated 02/09/2011).

Evaluation
Satisfactory, updated SmPC fragments and PIL were submitted in support of the variation application. The variation was approved on 28 May 2012 and the following updated SmPC fragments and PIL have been incorporated into the Marketing Authorisation.

Summary of Product Characteristics - updated

The SmPC fragments updated in-line with this variation are reproduced below:

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for infusion contains 2mg fluconazole.

Each 50 ml infusion bag contains 100mg fluconazole.
Each 100 ml infusion bag contains 200mg fluconazole.
Each 200 ml infusion bag contains 400mg fluconazole

Excipients
Also contains 15 mmol sodium per 100 ml dose.
For a full list of excipients, see section 6.1.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluconazole is indicated in the following fungal infections (see section 5.1).

Fluconazole is indicated in adults for the treatment of:
- Cryptococcal meningitis (see section 4.4)
- Coccidioidomycosis (see section 4.4)
- Invasive candidiasis
- Mucosal candidiasis including oropharyngeal, oesophageal candidiasis, candiduria and chronic mucocutaneous candidiasis
- Chronic oral atrophic candidiasis (denture sore mouth) if dental hygiene topical treatments are insufficient

Fluconazole is indicated in adults for the prophylaxis of:
- Relapse of cryptocoecal meningitis in patients with high risk of recurrence
Fluconazole is indicated in term newborn infants, infants, toddlers, children and adolescents aged from 0 to 17 years old:

Fluconazole is used for the treatment of mucosal candidiasis (oropharyngeal, oesophageal), invasive candidiasis, cryptococcal meningitis and the prophylaxis of candidal infections in immunocompromised patients. Fluconazole can be used as maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of recurrence (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.

Consideration should be given to official guidance on the appropriate use of antifungals.

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.

**Adults:**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Posology</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptococcosis</td>
<td>Treatment of cryptococcal meningitis</td>
<td>Loading dose: 400 mg on Day 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subsequent dose: 200 mg to 400 mg daily</td>
</tr>
<tr>
<td></td>
<td>Maintenance therapy to prevent relapse of</td>
<td>200 mg daily</td>
</tr>
<tr>
<td></td>
<td>cryptococcal meningitis in patients with high risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>of recurrence.</td>
<td>Indefinitely at a daily dose of 200 mg</td>
</tr>
<tr>
<td>Coccidioidomycosis</td>
<td></td>
<td>200 mg to 400 mg</td>
</tr>
<tr>
<td>Invasive candidiasis</td>
<td>Loading dose: 800 mg on Day 1</td>
<td>In general, the recommended duration of therapy for</td>
</tr>
<tr>
<td></td>
<td>Subsequent dose: 400 mg daily</td>
<td>candidemia is for 2 weeks after first negative blood</td>
</tr>
<tr>
<td>Treatment of mucosal</td>
<td></td>
<td>culture result and resolution of signs and symptoms</td>
</tr>
<tr>
<td>candidiasis</td>
<td>Oropharyngeal</td>
<td>attributable to candidemia.</td>
</tr>
<tr>
<td></td>
<td>Loading dose: 200 mg to 400 mg on Day 1</td>
<td>7 to 21 days (until oropharyngeal candidiasis)</td>
</tr>
<tr>
<td>Condition</td>
<td>Initial Dose</td>
<td>Subsequent Dose</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Candidiasis</td>
<td></td>
<td>Subsequent dose: 100 mg to 200 mg daily</td>
</tr>
<tr>
<td>Oesophageal candidiasis</td>
<td>Loading dose: 200 mg to 400 mg on Day 1</td>
<td>Subsequent dose: 100 mg to 200 mg daily</td>
</tr>
<tr>
<td>Candiduria</td>
<td>200 mg to 400 mg daily</td>
<td></td>
</tr>
<tr>
<td>Chronic atrophic candidiasis</td>
<td>50 mg daily</td>
<td>14 days</td>
</tr>
<tr>
<td>Chronic mucocutaneous candidiasis</td>
<td>50 mg to 100 mg daily</td>
<td></td>
</tr>
<tr>
<td>Prevention of relapse of mucosal candidiasis in patients infected with HIV who are at high risk of experiencing relapse</td>
<td>100 mg to 200 mg daily or 200 mg 3 times per week</td>
<td>An indefinite period for patients with chronic immune suppression</td>
</tr>
<tr>
<td>Prophylaxis of candidal infections in patients with prolonged neutropenia</td>
<td>200 mg to 400 mg</td>
<td>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 mm³</td>
</tr>
</tbody>
</table>

**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 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:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Percent of recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>100%</td>
</tr>
<tr>
<td>≤50 (no dialysis)</td>
<td>50%</td>
</tr>
<tr>
<td>Regular dialysis</td>
<td>100% after each dialysis</td>
</tr>
</tbody>
</table>
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 the 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 have not been studied in the paediatric population with renal insufficiency (for “Term newborn infants” who often exhibit primarily renal immaturity please see below).

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Posology</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal candidiasis</td>
<td>Initial dose: 6 mg/kg</td>
<td>Initial dose may be used on the first day to achieve steady state levels more rapidly</td>
</tr>
<tr>
<td></td>
<td>Subsequent dose: 3 mg/kg daily</td>
<td></td>
</tr>
<tr>
<td>Invasive candidiasis</td>
<td>Dose: 6 to 12 mg/kg daily</td>
<td>Depending on the severity of the disease</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of recurrence</td>
<td>Dose: 6 mg/kg daily</td>
<td>Depending on the severity of the disease</td>
</tr>
<tr>
<td>Prophylaxis of <em>Candida</em> in immunocompromised patients</td>
<td>Dose: 3 to 12 mg/kg daily</td>
<td>Depending on the extent and duration of the induced neutropenia (see Adults posology)</td>
</tr>
</tbody>
</table>

**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).

<table>
<thead>
<tr>
<th>Age group</th>
<th>Posology</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term newborn infants</td>
<td>The same mg/kg dose as for</td>
<td>A maximum dose of 12 mg/kg every 72 hours should not be exceeded</td>
</tr>
<tr>
<td>(0 to 14 days)</td>
<td>infants, toddlers and children</td>
<td></td>
</tr>
<tr>
<td></td>
<td>should be given every 72 hours</td>
<td></td>
</tr>
<tr>
<td>Term newborn infants</td>
<td>The same mg/kg dose as for</td>
<td>A maximum dose of 12 mg/kg every 48 hours should not be exceeded</td>
</tr>
<tr>
<td>(from 15 to 27 days)</td>
<td>infants, toddlers and children</td>
<td></td>
</tr>
<tr>
<td></td>
<td>should be given every 48 hours</td>
<td></td>
</tr>
</tbody>
</table>

**Method of administration**
Fluconazole may be administered either orally or by intravenous 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.
Intravenous infusion should be administrated at a rate not exceeding 10 ml/minute. Fluconazole is formulated in sodium chloride 9 mg/ml (0.9%) solution for infusion, each 200 mg (100 ml bottle) containing 15 mmol each of Na⁺ and Cl⁻. Because Fluconazole 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.

For instructions on handling of the product, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, to related azole substances or to any of the excipients (see section 6.1).

Co-administration 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 and erythromycin are contraindicated in patients receiving fluconazole (see sections 4.4 and 4.5).

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

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. Co-administration 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 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. Fluconazole 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 co-administration 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 0.15 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

**Concomitant use of the following other medicinal products is contraindicated:**

**Cisapride:** There have been reports of cardiac events including *torsades de pointes* in patients to
whom fluconazole and cisapride were co-administered. 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 QTc-interval. Concomitant
treatment with fluconazole and cisapride is contraindicated (see section 4.3).

**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 (see section 4.3). The co-administration of fluconazole at doses lower than
400 mg per day with terfenadine should be carefully monitored.
**Astemizole:** Concomitant administration of fluconazole with astemizole may decrease the clearance of astemizole. Resulting increased plasma concentrations of astemizole can lead to QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and astemizole is contraindicated (see section 4.3).

**Pimozide:** Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can lead to QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and pimozide is contraindicated (see section 4.3).

**Quinidine:** Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with QT prolongation and rare occurrences of *torsades de pointes*. Co-administration of fluconazole and quinidine is contraindicated (see section 4.3).

**Erythromycin:** Concomitant use of fluconazole and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsades de pointes*) and consequently sudden heart death. Co-administration of fluconazole and erythromycin is contraindicated (see section 4.3).

**Concomitant use of the following other medicinal products cannot be recommended:**

**Halofantrine:** Fluconazole can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4. Concomitant use of fluconazole and halofantrine has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsades de pointes*) and consequently sudden heart death. This combination should be avoided (see section 4.4).

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

**The effect of other medicinal products on fluconazole**

**Rifampicin:** Concomitant administration of fluconazole and rifampicin resulted in a 25% decrease in the AUC and a 20% shorter half-life of fluconazole. In patients receiving concomitant rifampicin, an increase of the fluconazole dose should be considered.

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

**The effect of fluconazole on other medicinal products**

Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. Fluconazole is also an inhibitor of the isozyme CYP2C19. In addition to the observed/documented interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9 and CYP3A4 coadministered with fluconazole. Therefore caution should be exercised when using these combinations and the patients should be carefully monitored. The enzyme inhibiting effect of fluconazole persists 4-5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole (see section 4.3).

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

**Amitriptyline, nortriptyline:** Fluconazole increases the effect of amitriptyline and nortriptyline. 5-nortriptyline and/or S-amitriptyline may be measured at initiation of the combination therapy and after one week. Dose of amitriptyline/nortriptyline should be adjusted, if necessary.
Amphotericin B: Concurrent administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small additive antifungal effect in systemic infection with *C. albicans*, no interaction in intracranial infection with *Cryptococcus neoformans*, and antagonism of the two medicinal products in systemic infection with *A. fumigatus*. The clinical significance of results obtained in these studies is unknown.

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

Benzodiazepines (short acting), i.e. midazolam, triazolam: Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. Concomitant intake of fluconazole 200 mg and midazolam 7.5 mg orally increased the midazolam AUC and half-life 3.7-fold and 2.2-fold, respectively. Fluconazole 200 mg daily given concurrently with triazolam 0.25 mg orally increased the triazolam AUC and half-life 4.4-fold and 2.3-fold, respectively. Potentiated and prolonged effects of triazolam have been observed after concomitant treatment with fluconazole. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dose, and the patients should be appropriately monitored.

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

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

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

Cyclophosphamide: Combination therapy with cyclophosphamide and fluconazole results in an increase in serum bilirubin and serum creatinine. The combination may be used while taking increased consideration to the risk of increased serum bilirubin and serum creatinine.

Fentanyl: One fatal case of fentanyl intoxication due to possible fentanyl fluconazole interaction was reported. Furthermore, it was shown in healthy volunteers that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression. Patients should be monitored closely for the potential risk of respiratory depression. Dosage adjustment of fentanyl may be necessary.

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

Immunosuppressors (i.e. ciclosporin, everolimus, sirolimus and tacrolimus):
**Ciclosporin:** Fluconazole significantly increases the concentration and AUC of ciclosporin. During concomitant treatment with fluconazole 200 mg daily and ciclosporin (2.7 mg/kg/day) there was a 1.8-fold increase in ciclosporin AUC. This combination may be used by reducing the dose of ciclosporin depending on ciclosporin concentration.

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

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

**Tacrolimus:** Fluconazole may increase the serum concentrations of orally administered tacrolimus up to 5 times due to inhibition of tacrolimus metabolism through CYP3A4 in the intestines. No significant pharmacokinetic changes have been observed when tacrolimus is given intravenously. Increased tacrolimus levels have been associated with nephrotoxicity. Dose of orally administered tacrolimus should be decreased depending on tacrolimus concentration.

**Losartan:** Fluconazole inhibits the metabolism of losartan to its active metabolite (E-3174) which is responsible for most of the angiotensin II-receptor antagonism which occurs during treatment with losartan. Patients should have their blood pressure monitored continuously.

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

**Non-steroidal anti-inflammatory drugs:** The Cmax and AUC of flurbiprofen was increased by 23% and 81%, respectively, when coadministered with fluconazole compared to administration of flurbiprofen alone. Similarly, the Cmax and AUC of the pharmacologically active isomer [S-(+)-ibuprofen] was increased by 15% and 82%, respectively, when fluconazole was coadministered with racemic ibuprofen (400 mg) compared to administration of racemic ibuprofen alone.

Although not specifically studied, fluconazole has the potential to increase the systemic exposure of other NSAIDs that are metabolized by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dose of NSAIDs may be needed.

**Phenytoin:** Fluconazole inhibits the hepatic metabolism of phenytoin. Concomitant repeated administration of 200 mg fluconazole and 250 mg phenytoin intravenously, caused an increase of the phenytoin AUC24 by 75% and Cmin by 128%. With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.

**Prednisone:** There was a case report that a liver-transplanted patient treated with prednisone developed acute adrenal cortex insufficiency when a three month therapy with fluconazole was discontinued. The discontinuation of fluconazole presumably caused an enhanced CYP3A4 activity which led to increased metabolism of prednisone. Patients on long-term treatment with fluconazole and prednisone should be carefully monitored for adrenal cortex insufficiency when fluconazole is discontinued.

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

**Saquinavir:** Fluconazole increases the AUC and Cmax of saquinavir with approximately 50% and 55% respectively, due to inhibition of saquinavir’s hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Interaction with saquinavir/ritonavir has not been studied and might be more marked. Dose adjustment of saquinavir may be necessary.
Sulfonylureas: Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulfonylureas (e.g., chlorpropamide, glibenclamide, glipizide, tolbutamide) in healthy volunteers. Frequent monitoring of blood glucose and appropriate reduction of sulfonylurea dose is recommended during coadministration.

Theophylline: In a placebo controlled interaction study, the administration of fluconazole 200 mg for 14 days resulted in an 18% decrease in the mean plasma clearance rate of theophylline. Patients who are receiving high dose theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole. Therapy should be modified if signs of toxicity develop.

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

Vitamin A: Based on a case-report in one patient receiving combination therapy with all-trans-retinoid acid (an acid form of vitamin A) and fluconazole, CNS related undesirable effects have developed in the form of pseudotumour cerebri, which disappeared after discontinuation of fluconazole treatment. This combination may be used but the incidence of CNS related undesirable effects should be borne in mind.

Voriconazole: (CYP2C9 and CYP3A4 inhibitor): Coadministration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 2.5 days) and oral fluconazole (400 mg on day 1, then 200 mg Q24h for 4 days) to 8 healthy male subjects resulted in an increase in Cmax and AUC of voriconazole by an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole associated adverse events is recommended if voriconazole is used sequentially after fluconazole.

Zidovudine: Fluconazole increases Cmax and AUC of zidovudine by 84% and 74%, respectively, due to an approx. 45% decrease in oral zidovudine clearance. The half-life of zidovudine was likewise prolonged by approximately 128% following combination therapy with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions. Dose reduction of zidovudine may be considered.

Azithromycin: An open-label, randomized, three-way crossover study in 18 healthy subjects assessed the effect of a single 1200 mg oral dose of azithromycin on the pharmacokinetics of a single 800 mg oral dose of fluconazole as well as the effects of fluconazole on the pharmacokinetics of azithromycin. There was no significant pharmacokinetic interaction between fluconazole and azithromycin.

Oral contraceptives: Two pharmacokinetic studies with a combined oral contraceptive have been performed using multiple doses of fluconazole. There were no relevant effects on hormone levels in the 50 mg fluconazole study, while at 200 mg daily, the AUCs of ethinyl estradiol and levonorgestrel were increased 40% and 24%, respectively. Thus, multiple dose use of fluconazole at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive.

4.6 Fertility, pregnancy and lactation

Pregnancy
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 undesirable effects in the foetus.

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 coccidiodomycosis. The relationship between fluconazole use and these effects is unclear.
Studies in animals have shown reproductive toxicity (see section 5.3).

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 (see section 5.3)

4.7 Effects on ability to drive and use machines

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 (see section 4.8) 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).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and the lymphatic system</td>
<td>Anaemia</td>
<td>Hypercholesterolaemia,</td>
<td></td>
</tr>
<tr>
<td>disorders</td>
<td></td>
<td>hypertriglyceridaemia,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>hypokalemia</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td>Anaphylaxis</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperkalemia</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Somnolence, insomnia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Seizures, paraesthesia,</td>
<td>Tremor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dizziness, taste</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>perversion</td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Vertigo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td>Torsade de pointes (see section 4.4),</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>QT prolongation (see section 4.4)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain,</td>
<td>Constipation dyspepsia,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>vomiting, diarrhoea,</td>
<td>flatulence, dry mouth</td>
<td></td>
</tr>
<tr>
<td></td>
<td>nausea</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Paediatric population:
The pattern and incidence of adverse reactions and laboratory abnormalities recorded during paediatric clinical trials are comparable to those seen in adults.

4.9 Overdose
There have been reports of overdose with Fluconazole and hallucinations 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.

As 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
ATC code: J02AC01
Pharmacotherapeutic group: Antimycotic for systemic use

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

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

Fluconazole also exhibits activity in vitro against \textit{Cryptococcus neoformans} and \textit{Cryptococcus gattii} as well as the endemic moulds \textit{Blastomyces dermatitidis}, \textit{Coccidioides immitis}, \textit{Histoplasma capsulatum} and \textit{Paracoccidioides brasiliensis}.

PK/PD relationship

In animal studies, there is a correlation between MIC values and efficacy against experimental mycoses due to \textit{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

\textit{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 \textit{Candida} species other than \textit{C. albicans}, which are often inherently not susceptible to fluconazole (e.g. \textit{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 \textit{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:

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>Species-related breakpoints (S&lt;/R&gt;)</th>
<th>Non-species related breakpoints (A)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>\textit{Candida albicans}</td>
<td>\textit{Candida glabrata}</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>2/4</td>
<td>IE</td>
</tr>
</tbody>
</table>

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

5.1 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 0.5-1.5 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 into 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 approximately 80% of the corresponding plasma levels.

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

The 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.

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 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 one study were not interpretable due to changes in formulation part way through the study. Additional data were available from a compassionate use study.

After administration of 2-8 mg/kg fluconazole to children between 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. 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 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 new-borns. The mean age at first dose was 24 hours (range 9-36 hours) and mean birth weight was 0.9Kg (range 0.75-1.10 Kg) for 12 pre-term neonates 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) was 1183 (range 1070-1470) on day 1 and increased, with time, to a mean of 1184 (range 1040-2130) 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 1.3 hours post-dose. The mean AUC was 76.4 ± 20.3 μg h/ml, and the mean terminal half-life was 46.2 hours. These pharmacokinetic parameter values are higher than analogous values reported for normal young male volunteers. Coadministration 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 hr, 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.

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 2-7 times the recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

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

There were no foetal effects at 5 or 10 mg/kg; increases in foetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg to 320 mg/kg embryolethality in rats was increased and foetal abnormalities included wavy ribs, cleft palate, and abnormal cranio-facial ossification.
The onset of parturition was slightly delayed at 20 mg/kg orally and dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg and 40 mg/kg intravenously. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. These effects on parturition are consistent with the species specific oestrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole (see section 5.1).
Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need it again.
- If you have any further questions, ask your doctor or nurse.
- The medicine has been prescribed for you. Do NOT pass it on to others. It may harm them even if their symptoms are the same as yours.
- If any of the side-effects gets worse, or if you notice any side-effects not listed in this leaflet, please tell your doctor or nurse.

Your medicine is called Fluconazole 2mg/ml Solution for Infusion (referred to as Fluconazole in this leaflet).

1. WHAT FLUCONAZOLE IS AND WHAT IT IS USED FOR

Flucanazole is one of a group of medicines called antifungal agents.

Flucanazole is used to treat infections caused by fungal and may also be used to stop you from getting candida infections. The most common cause of fungal infections is infection caused by Candida.

Adolescents (10 to 17 years old)

You might be given fluconazole if:
- you have a fungal infection caused by Candida (your immune system is weak and not working properly).

Children and adolescents (5 to 17 years old)

You might be given fluconazole if:
- you have a fungal infection caused by Candida (your immune system is weak and not working properly).
- stop cryptosporidium encephalitis from coming back.

2. BEFORE YOU ARE GIVEN FLUCONAZOLE INFUSION

You should not be treated with Fluconazole if you:
- you allergic (hypersensitive) to antifungal medicines, to other medicines you have been told to take for fungal infections or to any of the other ingredients of Fluconazole.
- have a fungal infection caused by Candida (your immune system is weak and not working properly).

Take special care with Fluconazole

Tell your doctor if you:
- have ever had diabetes.
- have heart disease.
- take other medicines for heart disorders.
- have any other medical conditions.

Taking other medicines

Tell your doctor immediately if you are taking aspirin, anticoagulants (for treating blood clots), antiinflammatory medicines, antihypertensive medicines or antibiotics (for treating infections) as these should not be taken with Fluconazole (see section ‘Do not take Fluconazole if you...’).

3. HOW FLUCONAZOLE INFUSION IS GIVEN

This medicine will be given by your doctor or nurse as a slow injection (infusion) into your vein.

Flucanazole is supplied as a solution: it will not be diluted further. There is more information for healthcare professionals in a section at the end of the leaflet.

The usual dose of this medicine for different infections are below, check with your doctor or nurse if you are not sure why you are being given Fluconazole.

4. POSSIBLE SIDE-EFFECTS

Flucanazole is usually given as a single dose of 150mg intravenously. There are some side-effects that may occur:
- vomiting.
- drug fever.
- allergic reactions (itching, rash, swelling of the skin, difficulty in breathing).

5. HOW TO USE YOUR MEDICINE

Intravenous Infusion should be administered at a rate not exceeding 15 minutes.

Flucanazole Infusion is formulated in sodium chloride 0.9% (9.0 g/L) solution for infusion admixtures containing 200 mg containing 5 mg each of Ha- and Co-80. Flucanazole is available as a sterile sodium chloride solution; in patients requiring sodium or fluid restriction, consideration should be given to the risks of fluid administration.
UKPAR Fluconazole 2 mg/ml Solution for Infusion

PL 24780/0003

Adolescents from 12 to 17 years old
Follow the dose prescribed by your doctor (either adults or children's posology).

Children: 1 to 11 years old
The maximum dose for children is 400 mg daily. The dose will be based on the child's weight or kilograms.

Condition Daily dose
Mucocutaneous and/or disseminated infections caused by Candida - dose and duration of the infection and on whether the infection is localized
3 mg per kg of body weight (6 mg per kg of body weight might be given on the 5th day)

Cryptococcal meningoencephalitis or internal fungal infections caused by Candida
6 mg to 12 mg per kg of body weight

To stop children from getting an infection caused by Candida (if the immune system is not working properly)
3 mg to 6 mg per kg of body weight

Use in children 0 to 4 weeks of age
Use in children of 3 to 4 weeks of age:
- The same dose as above but given once every 2 days. The maximum dose is 12 mg per kg of body weight every 48 hours.
- Use in infants less than 2 weeks old:
- The same dose as above but given once every 3 days. The maximum dose is 12 mg per kg of body weight every 72 hours.

Doctors sometimes prescribe different doses to these. Always take your medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Elderly
The usual adult dose should be given unless you have kidney problems.

Patients with kidney problems:
Your doctor may choose to lower your dose depending on your kidney function.

If you have been given more Fluconazole than you should
If you are concerned that you may have been given too much Fluconazole, tell your doctor or nurse immediately. The symptoms of a possible overdose may include heart racing, vomiting, and feeling sick that are not normal

If a dose of Fluconazole has been forgotten
As you will be given this medicine only by a doctor, close medical supervision is unlikely that a dose will be missed. However, tell your doctor or pharmacist if you think that a dose has been forgotten.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Fluconazole can cause side effects, although not everybody gets them.

A few people develop allergic reactions although serious allergic reactions are rare. If you get any of the following symptoms, see your doctor immediately:
- sudden widespread, difficulty breathing or tightness in chest
- swelling of eyes, lips or mouth
- itching all over the body, redness of the skin or itchy red spots
- skin rash
- severe skin reactions such as a rash that causes blebbling (this can affect the mouth and tongue).

Fluconazole may affect your liver. The signs of liver problems include:
- loss of appetite
- vomiting
- yellowing of your skin or the whites of your eyes (jaundice)

If any of these happens, stop taking Fluconazole and tell your doctor immediately.

Other side effects:
Additionally, if any of the following side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist:

Common side effects which affect 1 to 10 users in 100 are listed below:
- headache
- increase in blood levels of liver function
- rash
- stomach discomfort, diarrhea, feeling sick, vomiting

Uncommon side effects which affect 1 to 10 users in 1,000 are listed below:
- high blood pressure
- dehydration
- heavy feeling in the eyes
- dizziness, sensation of spinning, tingling or pricking, numbness, changes in sense of taste
- constipation, difficult digestion, wind, dry mouth
- muscle pain
- liver damage and yellowing of the skin and eyes
- wheezing
- tightness, general feeling of being uneasy, fever

Fluconazole may be infused through an existing line with one of the above listed fluids. Although no specific incompatibilities have been noted, mixing with any other medicinal products prior to infusion is not recommended.

The solution for infusion is for single use only.

From a microbiological point of view, the dilutions should be used immediately. If not used immediately, storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Rare side effects which affect 1 to 10 users in 10,000 are listed below:
- change in normal white blood cells that help defend against infections and blood cells that help to stop bleeding
- problems of low platelets, blood clotting and blood cell changes
- blood chemistry changes (high blood levels of cholesterol, fats)
- shaking, dizziness, abnormal electrocardiogram (ECG), change in heart rate or rhythm
- flatulence
- allergic reactions (sometimes severe), including widespread blisters, rash and skin peeling, severe skin reactions, swelling of the face or lips
- hair loss

If any of the side effects get serious or you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

5. HOW TO STORE FLUCONAZOLE INFUSION

Keep out of the reach and sight of children. Store in the original container. Do not refrigerate or freeze. Do not use unless the solution is clear and the container is undamaged. The solution may become cloudy, but this does not affect the quality of the medicine. Do not use Fluconazole infusion after the expiry date which is stated on the container and label. Once opened, the infusion will be used immediately and any unused solution will be thrown away. Medicines should not be disposed of via wastewater or household waste. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Fluconazole Solution for Infusion contains
The active ingredient is fluconazole (magnesium). The other ingredients are sodium chloride, sodium hydroxide and water for injection.

What Fluconazole Solution for Infusion looks like and the contents of each pack
Your medicine is a clear solution in a polyvinyl chloride (PVC) infusion bag, inside a polypropylene/aluminum/polyethylene/polyvinyl bag. Each 50mL, 100mL and 200mL infusion bag contains 100mg, 200mg and 400mg fluconazole respectively.

Marketing Authorisation Holder:
Hovione S.A., 40 Avenue Montebello, L-2149 Luxembourg.

Manufacturer:
Hovione, 40 Avenue Montebello, L-2149 Luxembourg.

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