Fluconazole 50 mg, 150 mg and 200 mg Capsules

PL 36390/0139-0141

UKPAR

TABLE OF CONTENTS

Lay Summary Page 2
Scientific discussion Page 3
Steps taken for assessment Page 12
Summary of Product Characteristics Page 13
Patient Information Leaflet Page 14
Labelling Page 15
LAY SUMMARY
Fluconazole 50 mg, 150 mg and 200 mg Capsules
(Fluconazole)

This is a summary of the Public Assessment Report (PAR) for Fluconazole 50 mg, 150 mg and 200 mg Capsules (PL 36390/0139-0141). It explains how Fluconazole 50 mg, 150 mg and 200 mg Capsules were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Fluconazole 50 mg, 150 mg and 200 mg Capsules.

For practical information about using Fluconazole 50 mg, 150 mg and 200 mg Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

What are Fluconazole 50 mg, 150 mg and 200 mg Capsules and what are they used for?
Fluconazole 50 mg, 150 mg and 200 mg Capsules contain the active substance fluconazole. They are used to treat infections caused by fungi (including yeasts such as one called Candida).

These products are identical to Fluconazole 50 mg, 150 mg and 200 mg Capsules (PL 40378/0165-0167), which are already authorised in the UK to Aptil Pharma Ltd.

How are Fluconazole 50 mg, 150 mg and 200 mg Capsules used?
Fluconazole 50 mg, 150 mg and 200 mg Capsules are taken orally. These medicines can be prescribed from the doctor.

The usual recommended doses depend on the type and severity of the infection.

Fluconazole is also available as a fluid that can be given directly into a vein to start the treatment off. This is then followed by the capsules.

How do Fluconazole 50 mg, 150 mg and 200 mg Capsules work?
Fluconazole is one of a group of medicines called anti-fungals. Fluconazole kills the fungi causing the infection by interfering with their cell membranes. It works by stopping the fungi from producing a substance called ergosterol, which is an essential component of fungal cell membranes. The disruption in production of ergosterol causes holes to appear in the fungal cell membrane. The cell membranes of fungi are vital for their survival. They keep unwanted substances from entering the cells and stop the contents of the cells from leaking out. As fluconazole causes holes to appear in the cell membranes, essential constituents of the fungal cells can leak out. This kills the fungi and treats the infection.

How have Fluconazole 50 mg, 150 mg and 200 mg Capsules been studied?
Fluconazole 50 mg, 150 mg and 200 mg Capsules are identical to previously granted applications for Fluconazole 50 mg, 150 mg and 200 mg capsules (Aptil Pharma Ltd; PL 40378/0165-0167). The company (Cipla (EU) Limited) referred to data provided
by Aptil Pharma Ltd for the grant of licences for Fluconazole 50 mg, 150 mg and 200 mg Capsules (Aptil Pharma Ltd; PL 40378/0165-0167) as a basis for the grant of licences for Fluconazole 50 mg, 150 mg and 200 mg Capsules (Cipla (EU) Limited; PL 36390/0139-0141).

**What are the benefits and risks of Fluconazole 50 mg, 150 mg and 200 mg Capsules?**
As Fluconazole 50 mg, 150 mg and 200 mg Capsules (Cipla (EU) Limited; PL 36390/0139-0141) are considered identical to Fluconazole 50 mg, 150 mg and 200 mg Capsules (PL 40378/0165-0167), their benefits and risks are taken as being the same as those for Fluconazole 50 mg, 150 mg and 200 mg Capsules (Aptil Pharma Ltd; PL 40378/0165-0167).

**Why are Fluconazole 50 mg, 150 mg and 200 mg Capsules approved?**
No new or unexpected safety concerns arose from these applications. It was, therefore, considered that the benefits of Fluconazole 50 mg, 150 mg and 200 mg Capsules outweigh their risks; and the grant of Marketing Authorisations were recommended.

**What measures are being taken to ensure the safe and effective use of Fluconazole 50 mg, 150 mg and 200 mg Capsules?**
A risk management plan has been developed to ensure that Fluconazole 50 mg, 150 mg and 200 mg Capsules are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Fluconazole 50 mg, 150 mg and 200 mg Capsules, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Fluconazole 50 mg, 150 mg and 200 mg Capsules
Marketing Authorisations were granted in the UK on 8th January 2014.

For more information about taking Fluconazole 50 mg, 150 mg and 200 mg Capsules, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in February - 2014.

The full PAR for Fluconazole 50 mg, 150 mg and 200 mg Capsules follows this summary.
Fluconazole 50 mg, 150 mg and 200 mg Capsules

PL 36390/0139-0141

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 5
Pharmaceutical assessment Page 6
Non-clinical assessment Page 9
Clinical assessment Page 10
Overall conclusion and risk benefit assessment Page 11
INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) for the medicinal products Fluconazole 50 mg, 150 mg and 200 mg Capsules (PL 36390/0139-0141) to Cipla (EU) Limited on 8th January 2014.

These prescription only medicines (POM) are indicated for the treatment of the following conditions when caused by fungi that are known or are likely to be fluconazole-susceptible:

1. Genital candidiasis. Vaginal candidiasis, acute or recurrent. Candidal balanitis. 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 (denture sore mouth). Normal hosts and patients with compromised immune function may be treated.
3. Systemic candidiasis including candidaemia, disseminated candidiasis and other forms of invasive candidal infection. These include infections of the peritoneum, endocardium and pulmonary and urinary tracts. Candidal infections in patients with malignancy, in intensive care units or those receiving cytotoxic or immunosuppressive therapy may be treated.
4. For the prevention of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, including bone marrow transplant patients.
5. Cryptococcosis, including cryptococcal meningitis and infections of other sites (e.g. pulmonary, cutaneous). Normal hosts and patients with AIDS, organ transplants or other causes of immunosuppression may be treated. Fluconazole can be used as maintenance therapy to prevent relapse of cryptococcal disease in patients with AIDS.
6. Tinea pedis, tinea corporis, tinea cruris, tinea versicolor and dermal Candida infections. Fluconazole is not indicated for nail infections and tinea capitis.

These applications were submitted as simple applications according to Article 10c of Directive 2001/83/EC, as amended. The applications are cross-referring to Fluconazole 50 mg, 150 mg and 200 mg capsules which were originally authorised to Neolab Limited (PL 08137/0101) on 13th February 2008. These reference products underwent Change of Ownership (CoA) procedures to APC Pharmaceuticals & Chemicals (Europe) Ltd (PL 32897/0005) on 11th February 2009 and then to the current Marketing Authorisation holder Aptil Pharma Ltd (PL 40378/0165-0167) on 16th October 2012.

No new data were submitted nor were they necessary for these simple applications, as the data are identical to those of the previously granted cross-reference products.
A summary of pharmacovigilance system and detailed Risk Management Plan have been provided with these applications. These are satisfactory.
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 36390/0139-0141
PROPRIETARY NAME: Fluconazole 50 mg, 150 mg and 200 mg Capsules
COMPANY NAME: Cipla (EU) Limited,
E.C. ARTICLE: Article 10c of Directive 2001/83/EC, as amended
LEGAL STATUS: POM

1 INTRODUCTION
These are informed consent applications for Fluconazole 50 mg, 150 mg and 200 mg Capsules, submitted under Article 10c of Directive 2001/83/EC, as amended. The applications are cross-referring to Fluconazole 50 mg, 150 mg and 200 mg capsules which were originally authorised to Neolab Limited on 13th February 2008. These reference products underwent Change of Ownership (CoA) procedures to APC Pharmaceuticals & Chemicals (Europe) Ltd on 11th February 2009 and then to the current Marketing Authorisation holder Aplit Pharma Ltd (PL 40378/0165-0167) on 16th October 2012. The current applications are considered valid.

2 MARKETING AUTHORISATION APPLICATION (MAA)
2.1 Name(s)
The proposed names of the products are Fluconazole 50 mg, 150 mg and 200 mg Capsules. The products have been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
The products are capsules for oral use and contain 50 mg, 150 mg and 200 mg of the active ingredient fluconazole.

The capsules are packed in blister strip composed of aluminium foil with white opaque PVC film-coated with PVdC. The pack sizes are 7 capsules (50 mg and 200 mg) and 1 capsule (150 mg).

The packaging and pack sizes are the same as those for the cross-reference products.

The proposed shelf-life is 2 years with storage conditions “Do not store above 25°C” and “Store in the original package”.

The shelf-life and storage conditions are identical to those for the cross-reference products and are satisfactory.

2.3 Legal status
These products are prescription only medicines (POM).

2.4 Marketing Authorisation Holder/Contact Persons/Company
The proposed Marketing Authorisation holder is Cipla (EU) Limited, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW
2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference products and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

2.6 Qualitative and quantitative composition
The proposed compositions are consistent with the details registered for the cross-reference products.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum full scale batch size is stated.

2.8 Finished product specifications
The proposed finished product specifications, at release and shelf-life, are in line with the details registered for the cross-reference products.

2.9 Drug substance specification
The proposed drug substance specification conforms to the current European Pharmacopoeia monograph for fluconazole and is in-line with that for the cross-reference products.

A European Directorate for the Quality of Medicines Healthcare (EDQM) Certificate of Suitability for the manufacture of fluconazole has been provided. The active substance manufacturer is the same as that for the cross-reference products.

2.10 TSE Compliance
The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

2.11 Bioequivalence
No bioequivalence data are required to support these informed consent applications, as the proposed products are manufactured to the same formula utilising the same process as the cross-reference products, Fluconazole 50 mg, 150 mg and 200 mg capsules (PL 40378/0165-0167).

3 EXPERT REPORTS
The applicant is cross-referring to the data for cross-reference products Fluconazole 50 mg, 150 mg and 200 mg capsules (PL 40378/0165-0167), to which it claims to be identical. This is acceptable. The applicant has included expert reports of the applications. Signed declarations and copies of the experts’ CVs are enclosed for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.
4. **PRODUCT NAME & APPEARANCE**
See 2.1 for details of the proposed product names. The appearance of the products is identical to those of the cross-reference products.

5. **SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)**
The proposed SmPCs are consistent with the details registered for the cross-reference products.

6. **PATIENT INFORMATION LEAFLET (PIL)/LABELLING**
User testing of the package leaflet has been accepted, based on a bridging report provided by the applicant making reference to the user-testing of the PIL for Fluconazole 50 mg and 200 mg capsules (PL 40378/0165 & 0167). This is acceptable for 150 mg strength as the PIL is simple in its instruction and worded the same way as the 150 mg reference PIL. A critical analysis demonstrated that the key messages for safe and effective use for all leaflets were similar with the exception of the column design. The justification of the rationale for bridging is accepted.

The proposed artwork complies with the relevant statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and sufficient space for a standard UK pharmacy dispensing label.

7. **CONCLUSION**
The data submitted with the applications are acceptable. The grant of Marketing Authorisations is recommended.
NON-CLINICAL ASSESSMENT

No new non-clinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

No new clinical data have been supplied with these applications and none are required for applications of this type.
OVERALL CONCLUSION AND BENEFIT RISK ASSESSMENT

QUALITY
The data for these applications are consistent with those previously assessed for the cross-reference products and as such, have been judged to be satisfactory.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
These applications are identical to the previously granted applications for Fluconazole 50 mg, 150 mg and 200 mg capsules (PL 40378/0165-0167) authorised to Aptil Pharma Ltd on 16th October 2012.

SAFETY
No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with those for the cross-reference products.

BENEFIT RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical concerns have been identified. The applicant’s products are identical to the cross-reference products. Extensive clinical experience with fluconazole is considered to have demonstrated the therapeutic values of the compounds. The benefit risk is, therefore, considered to be positive.
**Fluconazole 50 mg, 150 mg and 200 mg Capsules**

**PL 36390/0139-0141**

**STEPS TAKEN FOR ASSESSMENT**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation applications on 31\textsuperscript{st} December 2012</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 31\textsuperscript{st} January 2013</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information on 12\textsuperscript{th} April 2013 and 25\textsuperscript{th} October 2013</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s request, providing further information on 12\textsuperscript{th} September 2013 and 29\textsuperscript{th} November 2013</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 8\textsuperscript{th} January 2014</td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
UKPAR Fluconazole 50 mg, 150 mg and 200 mg Capsules

PL 36390/0139-0141

LABELLING

Keep out of the reach and sight of children.

Do not store above 25°C.

Store in the original package.

Read the package leaflet before use.

Take as directed by your doctor.

Always consult your doctor.

See leaflet for further information.

For oral use.

Fluconazole 50 mg Capsules
7 Capsules

Fluconazole 50 mg Capsules
Each capsule contains 50 mg Fluconazole

PL Holder:
Cipla (EU) Limited, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW.