IPAR

PUBLIC ASSESSMENT REPORT FOR A

MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Caneclear 150mg Capsule
Fluconazole
PA1113/013/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Caneclear 150mg capsules, from Phoenix Labs on the 18th December 2012 for

- Acute vaginal candidiasis when local therapy is not appropriate.
- Candidal balanitis when local therapy is not appropriate.

The application for Caneclear was submitted as a new national application.

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the HPRA's website at WWW.HPRA.IE

Name of the product	Caneclear 150mg Capsule
Name(s) of the active substance(s) (INN)	FLUCONAZOLE
Pharmacotherapeutic classification (ATC code)	J02AC01
Pharmaceutical form and strength(s)	150mg
Marketing Authorisation Number(s) in Ireland (PA)	PA 1113/013/001
Marketing Authorisation Holder	Phoenix Labs

II QUALITY ASPECTS

II.1. Introduction

This application is for Caneclear 150mg Capsules.

II.2 Drug substance

The active substance is fluconazole, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Hard gelatin, blue coloured, size "1" capsules.

Composition of the medicinal product is Fluconazole 150mg with following excipients:
Capsule contents: Lactose, Maize Starch, Colloidal silicon dioxide, Magnesium stearate, Sodium laurilsulfate
Capsule Shell: Patent blue V (E131), Titanium dioxide (E171), Methyl parahydroxybenzoate, Propyl parahydroxybenzoate, Gelatin.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients*)*

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for hard gelatine capsules, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented as a single capsule in a PVC blister pack with aluminium foil backing.

Evidence has been provided that the blister material complies with EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 3 years when stored below 25°C.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Caneclear 150mg Capsule.

III NON-CLINICAL ASPECTS

III.1 Non-clinical overview

The pharmacodynamic, pharmacokinetic and toxicological properties of fluconazole are considered well known. In view of the well established use of fluconazole, no new non- clinical studies have been performed. The non-clinical bibliographic overview on the pharmacology, pharmacokinetics and toxicology of fluconazole is thus considered adequate.

The non-clinical overview was written by an appropriately qualified expert. It contains a review of 16 references published from 1994-2006 and covers all appropriate non clinical aspects. The product literature (SmPC) is acceptable from a non-clinical perspective.

III.2 Ecotoxicity/environmental risk assessment

Fluconazole is not a new drug substance and has been authorised in the EU for more than 10 years.
A justification has been provided for the absence of a formal environmental risk assessment based on the expectation that the introduction of this product onto the market is unlikely to result in an increase in the environmental exposure of fluconazole.

III.3 Discussion on the non-clinical aspects

There are no objections to the approval of Caneclear 150mg Capsule from a non-clinical perspective.

IV CLINICAL ASPECTS

IV.6 Discussion on the clinical aspects

Caneclear 150mg oral capsule is identical in formulation to other 150 mg oral fluconazole products available in the European market. This application has thus been a bibliographic submission in accordance with Article 10a (well-established use) of Directive 2001/83/EC.
The antifungal activity of fluconazole is well known. Its spectrum of antimicrobial efficacy is well described and it remains active against most Candida species. Efficacy has been demonstrated in randomised controlled trials and other clinical settings. Its availability in a single oral dose of 150 mg capsule makes fluconazole a safe and effective treatment for genital candidiasis due to susceptible Candida species. Due to its interaction with many other drugs in routine clinical practice and its potential for adverse effects, a judicious use of the drug is advised. At the recommended dose, significant adverse effects are very rare, and Caneclear 150 mg is considered a safe and effective treatment of genital candidiasis, namely, vulvovaginal candidiasis in women candidal balanitis and in men when other treatments are not appropriate.
The content of the SmPC approved for Caneclear 150mg is in accordance with that accepted for the SmPC, package leaflet and labelling agreed during the finalised Article 30 referral procedure for Diflucan 150mg.
The risk-benefit evaluation of Caneclear 150 mg is therefore considered to be positive.

IV.1 Introduction

The basis of the application is that the constituent of the medicinal product (fluconazole) has a well established medicinal use with recognised efficacy, and an acceptable level of safety (pursuant to Article 10a of Directive 2001/83/EC as amended by Directive 2004/27/EC). The clinical basis of the submission rests therefore on bibliographical evidence of the efficacy and safety of fluconazole in the proposed indications. Fluconazole has been very widely studied. Evidence to support the safety and efficacy of fluconazole in the proposed indications will be presented in this overview.

IV.2 Pharmacokinetics

Fluconazole is a semi-synthetic azole designated an imidazole due to the presence of three nitrogen atoms on the azole ring, which is active against numerous yeasts, but not filamentous fungi. It acts by the inhibition of C-14 a demethylase which is required for ergo- sterol synthesis, an essential building block of fungal cell membrane.

Fluconazole is characterised by high oral bioavailability (over 80%) and widespread distribution into body fluids and tissues. Peak levels are reached in 0.5 to 1.5 h in healthy fasting adults and gastrointestinal absorption is not influenced by the gastric pH. The long half life (27–34 h) in adult population supports once daily administration. Fluconazole is poorly metabolised and the majority is excreted as unchanged medicinal product in the urine via the kidneys (60–75%) (Charlier 2006). A single tablet of 150 mg fluconazole administered once weekly achieves highly inhibitory and fungistatic concentrations in the vagina for at least four days. Levels in breast milk are 50-90% of those found in plasma, but the extent to which fluconazole crosses the placenta is not known.

Fluconazole is metabolised via the liver and the cytochrome P450 (CYP450) family of enzymes.

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 of the SmPC). Fluconazole is also an inhibitor of the isozyme CYP2C19.

There is a risk of increased plasma concentrations of other medicinal products metabolised by CYP2C9 or CYP3A4 (e.g. ergot-alkaloids, quinidine) when co-administered with fluconazole. The enzyme-inhibiting effect of fluconazole may persist for 4-5 days after the end of fluconazole treatment due to the long fluconazole half-life. 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 CYP 3A4 such as cisapride, astemizole, pimozide, quinidine and erythromycin are contraindicated in patients receiving fluconazole .The current SmPC outlines the potential interactions that could occur when fluconazole is co administered with other medicines metabolised by CYP2C9 CYP2C19 or CYP3A4.

IV.3 Pharmacodynamics

Fluconazole has a fungistatic effect, which specifically inhibits the synthesis of the fungi's ergosterol, which is believed to lead to defects in the cell membrane. In vitro, fluconazole displays antifungal activity against most clinically common Candida species (including C. albicans, C. tropicalis, C. parapsilosis,). It exhibits less activity against C. krusei and C. guilliermondi and variable activity against C.glabrata.
Fluconazole also exhibits activity in vitro against Cryptococcus neoformans and Cryptococcus gattii as well as the endemic moulds Blastomyces dermatiditis, Coccidioides immitis, Histoplasma capsulatum and Paracoccidioides brasiliensis.

No other significant pharmacodynamic effects have been identified in humans with single doses of 150 mg. A single tablet of 150 mg fluconazole administered once weekly achieves highly inhibitory and fungistatic concentrations in the vagina for at least four days and is effective in treating uncomplicated vulvovaginal candidiasis caused by C. albicans in immunocompetent women.

Resistance

Candida species have developed a number of resistance mechanisms to azole antifungal agents. Fungal strains which have developed one or more of these resistance mechanisms are known to exhibit high minimum inhibitory concentrations (MICs) to fluconazole which impacts adversely efficacy *in vivo* and clinically.

There have been reports of superinfection with Candida species other than C. albicans, which are often inherently not susceptible to fluconazole (e.g. Candida krusei). Such cases may require alternative antifungal therapy.
The emergence of strains of Candida species resistant to fluconazole has become increasingly important but it is generally restricted to immunocompromised patients receiving long-term prophylaxis with fluconazole.

IV.4 Clinical Efficacy

No new clinical data have been supplied with this application and none are required for an application of this type. The efficacy and safety of Caneclear 150 mg Capsule in the treatment of acute or vaginal candidiasis and candidal balanitis in this application is based on bibliographic evidence. An extensive clinical database is available in the public domain for fluconazole, and was reviewed in the detailed Clinical Overview presented with this application.

Epidemiology

Information on the incidence of vulvovaginal candidiasis is incomplete, since the disease is not a reportable entity and data collection is limited by inaccuracies of diagnosis and the use of non-representative study populations. However it is reported that the infection, caused by Candida species, affects 70-75% of women at least once during their lives, most frequently young women of childbearing age. 40-50% of women will experience a recurrence. 5-8% of adult women have recurrent vulvovaginal candidiasis, defined as four or more episodes every year. (Sobel JD 2007)

Vulvovaginal candidiasis

Fluconazole administered as a single 150 mg oral dose proved to be as safe and effective as 7 days of intravaginal clotrimazole therapy for Candida vaginitis during a multicentre, randomized, prospective, single-blinded study of 429 patients. The authors in this study felt that the therapy of vaginitis should be individualized, taking into consideration severity of disease, history of recurrent vaginitis, and patient preference. (Sobel JD et al 1995)

A study aimed at evaluating the accuracy of clinical diagnosis by comparing it with microbiologic test results, and to determine the causative agents of vaginal infections has concluded that the clinical diagnosis of vaginal infection is inadequate and should be confirmed with microbiological testing if the resources are available (Karaca et al 2007). Diagnosis of vulvovaginal candidiasis requires a correlation of clinical findings, microscopic examination, and vaginal culture. There is no reliable serological or antigen detection technique available for the diagnosis of vulvovaginal candidiasis.

The majority of cases of acute symptomatic vulvovaginal candidiasis are caused by Candida albicans, but in recent years an increase has been observed in the frequency of non-albicans Candida infections, especially due to C. glabrata and C. tropicalis. Between 85% and 95% of yeast strains isolated from the vagina belong to the species Candida albicans. The remainders are non-albicans Candida species, the most common of which is Candida glabrata. However in some parts of the world, non-albicans isolates, notably C glabrata, affect 10-20% of women. Susceptibility testing performed on vaginal yeast isolates collected from January 1998 to March 2001 from 429 patients with suspected vulvovaginal candidiasis identified C. albicans as the most common species associated with vulvovaginitis (76%), followed by C. glabrata (16%). The overall percentage of non-albicans vaginitis (24%) was higher than in previous reports. Both topical antifungals and oral fluconazole was found to have excellent activity versus *C. albicans*, but less activity versus non-albicans species. (Richter S et al, 2005)

In 1999 Edelman et al. conducted a search of the medical literature which identified 14 studies that compared single-dose therapy for vaginal candidiasis in non-pregnant women. In eight of these studies, fluconazole 150 mg orally was one of the treatments studied. Other treatments studied included clotrimazole, econazole, itraconazole, miconazole, terconazole and fenticonazole. These studies, conducted according to similar study designs, evaluated clinical and mycologic cure rates. There were few significant differences in either the clinical or mycologic cure rates of single-dose therapy, and no one therapy was consistently better than any other (Edelman et al 2009).

In a review of 19 trials that assessed the relative effectiveness of oral versus intra-vaginal anti-fungals for the treatment of uncomplicated vulvovaginal candidiasis the authors concluded that no statistically significant differences were observed in clinical cure rates of anti-fungals administered by the oral and intra-vaginal (topical) routes for the treatment of uncomplicated vaginal candidiasis. No definitive conclusion could be made regarding the relative safety of oral and intra-vaginal anti-fungals for uncomplicated vaginal candidiasis. (Nurbai M et al Cochrane Collaboration 2009).

Single dose fluconazole is well established as an effective treatment for uncomplicated vulvovaginal candidiasis.

<u>Candidal Balanitis</u>

Candidal Balanitis is clinically diagnosed and can be confirmed by laboratory tests. (Edwards et al 2001) A pilot open non-comparative study suggests that single oral dose of 150 mg fluconazole is an effective, well tolerated and convenient treatment for men presenting with symptomatic candidal balanitis. A total of 14 men presenting with preputial soreness and signs of erythema of the glans and prepuce, who were culture-positive for Candida albicans entered into this study. One patient was an insulin-dependent diabetic and another had recently been treated with antibiotics for a sore throat; none of the others had predisposing systemic or local conditions.
All 11 of the patients who returned for follow-up evaluation 7-10 days later were found to be mycologically cured. All were symptomatically improved. No side effects were reported by any of the patients. (Kinghorn et al 1990)

In another study in an outpatients' centre in Austria, single oral dose of 150 mg fluconazole has been found to be of comparable efficacy and safety to clotrimazole cream in patients with balanitis. (Stary et al 1996) The randomized, open-label parallel-group multicentre study compared 64 patients treated with 150 mg oral fluconazole and 68 with clotrimazole applied topically twice daily for 7 days.

At short term follow up, 92% and 91% respectively were clinically cured or improved. Candida albicans was eradicated in 78% and 83% of patients respectively. Median time to relief of erythema was 6 days for fluconazole and 7 days for clotrimazole. Twelve of 15 patients who had received previous topical therapy for balanitis said they preferred oral therapy. At the one month follow up visit, 24/36 and 29/33 patients in the two groups were clinically cured or improved. Nine in the fluconazole group experienced a relapse; 6 of these 9 patients reported previous episodes of this infection during the past year. Two patients in the clotrimazole group had a relapse; neither had a history of previous episodes. Mycological eradication was noted in 26/36 and 25/33 patients in the two groups. Both treatment regimens were well tolerated.

During a recent referral under Article 30 of Directive 2001/83/EC for the 150 mg, one capsule presentation for Diflucan (fluconazole) it was noted that the indication for genital candidiasis and more specifically vulvovaginal candidiasis in adult women and candidal balanitis in adult men was authorised in some member states for the 150 mg, one capsule presentation due to the convenience of one dose treatment. The CHMP accepted that the data presented by the marketing authorisation holder was satisfactory for these indications. However as the first line treatment of uncomplicated candidiasis and candidal balanitis is topical application of an antifungal, the one 150 mg capsule presentation was specifically indicated for the genital candidiasis indications in adults when local therapy was not appropriate.

For the one 150 mg capsule presentation the section 4.1 of the SPC was agreed by the CHMP as follows:

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

- *Acute vaginal candidiasis when local therapy is not appropriate.*
- *Candidal balanitis when local therapy is not appropriate.*

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.

Section 4.1 of the SPC for Caneclear 150mg has been updated inline with the outcome of this Article 30 referral procedure.

IV.5 Clinical Safety

The applicant has submitted a risk management plan outlining the known safety profile of fluconazole. As this product has been available for many years and is used extensively globally, no further safety procedures beyond normal pharmacovigilance activities are required to monitor the safety of the product.

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance System, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

Safety Overview

The application is a bibliographic submission for a generic product and so there are no extensive company generated clinical trial data. Supportive information for the well-characterised safety profile comes from published articles on fluconazole.

Fluconazole is generally well tolerated. Common side effects include headache, nausea, vomiting, diarrhea, abdominal pain and raised alanine aminotransfersase (ALAT). Other rarer side effects do occur especially with doses > 400 mg/day or in patients with significant comorbidity. (Charlier C 2006). 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.

Hepatic system

Severe hepatic toxicity, including death, has been reported in rare cases, primarily in patients suffering from serious underlying diseases. No obvious relationship between hepatotoxicity and total daily dose of fluconazole, duration of therapy, gender or age of the patient has been observed. The benefits of the treatment should be evaluated against the risks of developing serious liver damage if therapy is continued in patients whose liver enzyme values rise during fluconazole treatment. Fluconazole should be discontinued if clinical signs or symptoms consistent with liver disease develop during treatment.

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.

Cardiovascular system

Some azoles have been associated with QT-interval prolongation. This includes fluconazole, which is listed by the WHO as the causative agent of Torsades de Pointes (TdP). TdP occurs with a low frequency, but is however, potentially life threatening. There is a lack of knowledge on the predictability of TdP despite known risk factors, and thus the true incidence rate is not known. (EMEA/CPMP/6236/04 Fluconazole Tiefenbacher). 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 arrhythmias
•Concomitant medication not metabolised by CYP3A4 but known to prolong QT interval.

Drug- induced TdP may be mediated through a primary drug effect, by blocking the repolarising outward current IKr (hERG channel). Drug induced TdP may also occur as a secondary drug effect mediated through repolarisation modifying factors such as hypokalaemia, bradycardia, gender, heart failure or through pharmacokinetic interactions when for instance an inhibitor of a CYP450 metabolic enzyme is co- administered with a QT prolonging drug which is a substrate of this enzyme, or other metabolic factors, such as liver or renal disease. Case reports indicate that fluconazole might have the potential to induce QT prolongation leading to serious cardiac arrhythmia. Patients treated concurrently with fluconazole and other drugs that prolong QT interval should be carefully monitored, since an additive effect can not be excluded.

Fluconazole use in special populations

Pregnancy and lactation

Data from several hundred pregnant women treated with standard doses (below 200 mg/day) of fluconazole, administered as a single or repeated dose during the first trimester; do not indicate undesirable effects on the foetus. Five cases of high-dose treatment have been identified, resulting in malformations in 4/5 live births. The malformations in all four cases seem consistent with the pattern described as the Antley-Bixler syndrome. Antley-Bixler syndrome is a rare disorder characterized by craniosynostosis, midface hypoplasia, radiohumeral synostosis, joint contractures, arachnodactyly, and femoral bowing and fractures.
The population-based Pharmaco-Epidemiological Prescription Database of the County of North Jutland, Denmark, initiated on 1 January 1991, was used to identify 176 prescriptions for all singleton pregnant women in the county who gave birth in the period from 1991 to 1996. A total of 165 pregnant women exposed to fluconazole around conception and/or in pregnancy were identified. The control group consisted of 13,327 women who did not receive any reHPRAursed prescription 30 days before or during their pregnancies. The prevalence proportion of malformation was 3.3% in the exposed and 5.2% in the control group. No elevated risk of malformation was found (odds ratio: 0.65, 95% confidence limits: 0.24-1.77). (Sorensen 1999).
A prescription-event monitoring study with special reference to the outcome of pregnancy concluded that fluconazole, is a safe and effective treatment for vaginal candidiasis (Inman et al 1994).

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. If treatment is imperative in adolescents (from 12 to 17 years old), the posology should be the same as for adults.

Elderly

For patients above 60 years of age fluconazole can be used strictly under medical supervision at the same dosage as for adults.

Renal impairment

Fluconazole is predominantly excreted in the urine as unchanged active substance. No adjustments in single dose therapy are necessary.

Hepatic impairment

Limited data are available in patients with hepatic impairment, therefore fluconazole should be administered with caution to patients with liver dysfunction.

V OVERALL CONCLUSIONS

Benefit/Risk Assessment and Recommendations

The HPRA, on the basis of the data submitted, considered that Caneclear 150mg oral capsule demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation

VII UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
Transfer	PA1113/013/001	MAH & PA No.	11/03/2016	16/03/2016