# IPAR

# Public Assessment Report for a Medicinal Product for Human Use

Scientific discussion

Canesten Soft Vaginal Capsule Combi 500mg Soft Vaginal Capsule and 2% w/w Cream
CLOTRIMAZOLE
PA1410/039/014

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.

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# I INTRODUCTION

## INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Canesten Soft Vaginal Capsule Combi, from Bayer Limited on 24th March 2016 for the treatment of candidal vaginitis.

This application for a marketing authorisation was submitted as a line extension to the existing Canesten Combi Pessary & Cream with the legal basis, Article 8(3) of Directive 2001/83/EC. The clinical data submitted demonstrate non-inferiority for the soft vaginal capsule compared to the pessary.
Considering that the line extension is based on the currently licensed combination pack Canesten Combi Pessary & Cream the documentation focuses on the comparative assessment of the clotrimazole 500 mg vaginal capsule versus clotrimazole 500 mg vaginal tablet (pessary). Canesten 500mg Soft Vaginal Capsule, - PA1410/039/010 - CRN 2113686 was approved as separate line extension on the 12/12/2014.
In line with Canesten Combi Pessary & Cream this product will be non-prescription and for supply through pharmacies only.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

| | |
|---|---|
| Name of the product | Canesten Soft Vaginal Capsule Combi |
| Name(s) of the active substance(s) (INN) | CLOTRIMAZOLE |
| Pharmacotherapeutic classification (ATC code) | G01AF02 CLOTRIMAZOLE |
| Pharmaceutical form and strength(s) | Capsules, Soft 500mg/2%w/w Cream |
| Marketing Authorisation Number(s) in Ireland (PA) | PA1410/039/014 |
| Marketing Authorisation Holder | Bayer Limited |

# II QUALITY ASPECTS

## II.1. Introduction

This application is for Canesten Soft Vaginal Capsule Combi 500mg Soft Vaginal Capsule and 2% w/w Cream.

## II.2 Drug substance

The active substance is clotrimazole 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

Each soft vaginal capsule contains 500mg clotrimazole.
Each gram of cream contains 20mg clotrimazole (equivalent to 2% w/w).

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is consists of two established pharmaceutical forms 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/*Ancillary Substances*)

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 the relevant dosage forms, 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 approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur. and 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 and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

## 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 Canesten Soft Vaginal Capsule Combi 500mg Soft Vaginal Capsule and 2% w/w Cream.

# III NON-CLINICAL ASPECTS

## III.1 Introduction

This product is an extension of the existing clotrimazole 500 mg Pessary (Vaginal Tablet) & 2% Cream. This active substance has been available on the Irish market for more than 10 years.

No new non-clinical data has been submitted. Pharmacodynamic, pharmacokinetic and toxicological properties of clotrimazole are well known. Non-clinical data have been superseded by clinical experience and therefore no new non-clinical data are required to support the application.

## III.2 Pharmacology

Clotrimazole is a potent antimycotic that acts against fungi by inhibiting ergosterol synthesis, which in turn leads to structural and functional impairment of the cytoplasmic membrane resulting in leakage of intracellular phosphorus compounds with a concomitant breakdown of cellular nucleic acids and potassium efflux. Clotrimazole has a broad spectrum of antimycotic action: along with dermatophytes and moulds, yeasts are particularly sensitive to clotrimazole *Candida albicans, Candida tropicalis*, and *Candida parapsilosis* are reported to be susceptible to all azoles, while other non-*albicans* species have higher minimum inhibitory concentration (MIC) values.

## III.3 Pharmacokinetics

The non-clinical pharmacokinetics of non-labelled and of 14C-labelled clotrimazole were studied in various animal species (mouse, rat, dog, rabbit) using various dosage forms and routes of administration. In addition to studies utilising oral and intravenous administration clotrimazole has been used as aerosol, topical cream, intravaginal cream and intravaginal pessary.

Topical or intravaginal application results in lower plasma concentrations than after oral administration (ng/ml for the vaginal route vs. µg/ml range for the oral route. The systemic fate of clotrimazole is well characterised. Clotrimazole is transferred across the placenta of pregnant rats to a small extent. Due to the high solubility of clotrimazole in lipids the concentrations in milk were higher than those in blood. The binding of clotrimazole to proteins of human blood plasma is very high. About 98% are bound to plasma proteins.

## III.4 Toxicology

Acute oral toxicity was moderate with no gender differences. Repeat dose toxicity was tested in rat and dog studies

There is no evidence to suggest that clotrimazole is mutagenic or genotoxic

The carcinogenic potential of clotrimazole has been investigated in the rat following oral administration with no evidence of carcinogenic potential.

Reproduction and/or developmental toxicity studies were conducted using oral route of clotrimazole administration in frogs, mice, rats, and rabbits. No effects on fertility, or signs of embryo-foetotoxicity, or teratogenicity were evident.

Subacute studies in dogs and monkeys as well as dermal application in rabbits showed no evidence of treatment-related local adverse effects.

## III.5 Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment has not been performed. This product is an additional registration of a clotrimazole 500 mg Soft Vaginal Capsule & 2% Cream as an extension of the existing clotrimazole 500 mg Pessary & 2% Cream is not expected to result in a significant increase of the use of the clotrimazole based formulations and thus no increase is assumed of the environmental concentration of clotrimazole.

### III.6 Discussion on the non-clinical aspects

The non-clinical overview on the preclinical pharmacology, pharmacokinetics and toxicology is acceptable. Non-clinical findings are adequately mentioned in the appropriate sections of the SmPC.

## IV CLINICAL ASPECTS

### IV.1 Introduction

This is a line extension application through a national procedure submitted in accordance with the legal basis, Article 8 (3) of Directive 2001/83/EC to the combination pack Canesten Combi PA1410/039/001 (clotrimazole 500 mg vaginal tablet (pessary) & clotrimazole 2% cream).
In this application the clotrimazole 500 mg pessary is replaced by a clotrimazole 500 mg soft vaginal capsule. Canesten 500mg Soft Vaginal Capsule, - PA1410/039/010 was licensed separately on 12/12/2014.
The second component of the new combination pack, clotrimazole 2% cream, is completely identical with the originator product.

Clotrimazole 2% cream is used concomitantly with one clotrimazole 500 mg vaginal capsule to treat the infections of the labia and adjacent areas until symptoms disappear (candidal vulvitis). It is indicated as well to treat the inflammation of the glans and prepuce of the sexual partner caused by yeast fungi (candidal balanitis). Clotrimazole 500 mg soft vaginal capsules and pessary are applied intravaginally once at bedtime by the use of an applicator and the 2% cream is applied externally to the vulva and surrounding areas.

In this line extension application, the applicant submitted an investigator-blinded study showing the non-inferiority of the new clotrimazole soft vaginal capsule formulation (500 mg) versus the long-standing approved clotrimazole vaginal tablet (500 mg) in the treatment of vulvovaginal mycosis. In addition to the non-inferiority clinical study regarding safety and efficacy of clotrimazole 500 mg vaginal capsules in comparison with the clotrimazole 500 mg vaginal tablet in the originator product, the present documentation also refers to the originator information. The applicant also conducted a review of relevant scientific literature on clotrimazole. The clinical data provided demonstrated non-inferiority for the clotrimazole 500mg soft vaginal capsule compared to the originator product clotrimazole 500 mg vaginal tablet. The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

### IV.2 Pharmacokinetics

The pharmacokinetic profile of clotrimazole has been adequately reflected in the originator documentation and is cross referred to in this application. Other pharmacokinetic data were discussed for supplementary information, but are considered to be of secondary relevance. In a clinical trial, an increased exposure to tacrolimus was observed during daily treatment with buccal/oral clotrimazole over 7 days in renal transplant recipients suggestive of enzyme inhibition (CYP3A4) or P-glycoprotein in the gut wall. A similar interaction is suspected for sirolimus. No data on drug interactions additional to those already summarised and discussed within the original documentation are known.

Pharmacokinetic drug interactions overall appear unlikely in face of the relatively low absorption of vaginal clotrimazole and were not observed during the long-term clinical experience available for locally applied clotrimazole.

### IV.3 Pharmacodynamics

Clotrimazole acts principally by inhibiting the CYP450-dependent lanosterol-14α-demethylase (CYP51), inhibiting the synthesis of ergosterol, an essential component in the fungal membrane. Clotrimazole has a broad spectrum of antimycotic action. The efficacy of clotrimazole is concentration-dependent.

## IV.4 Clinical Efficacy

The applicant has conducted an investigator-blinded, 2-arm, multicentre, randomised clinical trial to compare the safety and efficacy of clotrimazole 500mg soft vaginal capsules with the originator standard clotrimazole 500mg vaginal tablets after a single dose in women with vulvovaginal mycosis**.**
The primary efficacy objective was the overall response rate at visit 2 (10 -14 days) comprising of the two parameters clinical cure and mycological cure.
A clinical cure was defined as an absence of the symptoms itching and burning/ irritation, and no more than mild expressions of other symptom and no worsening of any symptoms and signs compared to baseline visit. A mycological cure was defined as negative microscopy and negative mycological culture.
Secondary efficacy parameters (main analyses based on the ITT population) were the overall response at visit 3(6-8 weeks) and the clinical and mycological cure rates at visit 2 and 3, which were also analysed for non inferiority.

Analysis of overall response (responder rate at visit 2) was performed by deriving a two-sided 95%-confidence interval the difference of response rates of the tablet and the ovule. Noninferiority of the soft vaginal capsule formulation was concluded when the lower 95% confidence interval was greater than the observed response rate of the vaginal tablet (-15%).

A total of 465 women between the ages of 14 and 50 years were randomised and 463 patients received treatment. At screening/baseline (visit 1) clinical symptoms (itching, burning/irritation, discharge, dysuria) and signs (vaginal edema, erythema and excoriation, and vulval edema, erythema and excoriation) of a vaginitis were assessed and a mycological testing was performed. If the baseline mycological culture was negative the subject was to be withdrawn at visit 2 (10-14 days after visit 1) and was excluded from the main efficacy analysis. A total of 117 (25%) subjects were prematurely withdrawn from the study and the main reason for premature withdrawal (17 %) was non-confirmation of mycosis by mycological culture.

**Overall response at visit 2 and visit 3 (primary efficacy parameter)**

A total of 123/186 subjects of the tablet (66.1%) and 132/180 women of the capsule group (73.7%) had responded to treatment at visit 2 (overall response i.e. clinical and mycological cure, primary efficacy objective).The difference between the treatments was small and non-significant (p=0.33). These results were confirmed in the ITT analysis.

**Overall response at visit 2 (primary efficacy parameter)**
**Per protocol (PP) population**

| | - Tablets - N=186 n (%) | - Ovules - N=180 n (%) |
|---|---|---|
| Number of responders (n (%)) | 123 (66.1%) | 132 (73.3%) |
| 95% CI | (59.2%, 73.2%) | (66.6%, 80.1%) |
| Difference ovules-tablets (95% CI) | 7.2% (-7.3%, 21.7%) | |

CI = confidence interval
Source: Table 14.2.1.1

At visit 3 the overall response rate was similar to visit 2 in the ovule group (129/178 subjects (72.5%) were responders) and slightly higher than at visit 2 in the tablet group (138/184 subjects (75.0%)). The difference between the two treatment groups was low (-2.5%) and not statistically significant p=0.73. Non-inferiority of the ovule formulation was demonstrated. Similar results were seen for the PP analysis.

**Overall response at visit 3 (ITT population)**

| | - Tablets - N=192 n (%) | - Ovules - N=185 n (%) |
|---|---|---|
| Number of subjects with available data | 184 | 178 |
| Number of responders (n (%)) | 138 (75.0%) | 129 (72.5%) |
| 95% CI | (68.5%, 81.5%) | (65.6%, 79.3%) |
| Ovules-tablets (95% CI) | -2.5% (-16.7%, 11.7%) | |

CI = confidence interval
Source: Table 14.2.1.1

Most subjects in both treatment groups were free of signs or symptoms of vaginitis at 2 weeks after treatment. The responder rates were similar for both treatment groups (the cure rates were 84.4% and 88.1% for clinical symptoms and 96.9% and 98.4% for signs of vaginitis for the tablet and ovule group, respectively). At 6 to 8 weeks after drug administration the cure rates for clinical symptoms further increased in both treatment groups and remained similar for the signs of vaginitis. Differences between the two treatment groups were again without clinical or statistical significance and the ovule formulation proved to be non-inferior to the tablet formulation (p=0.36 or higher).

**Response rates for clinical signs and symptoms and for mycological cure (ITT population)**

| | **Tablets n = 192 (%)** | **Capsules n = 185 (%)** | **Tablets n = 192 (%)** | **Capsules n = 185 (%)** |
|---|---|---|---|---|
| **Clinical symptoms** | Visit 2 | | Visit 3 | |
| Subjects with available data (n) | 192 | 185 | 185 | 180 |
| Number of responders, n (%) | 162 (84.4%) | 163 (88.1%) | 172 (93.0%) | 167 (92.8%) |
| 95% CI | 79.0%, 89.8% | 83.2%, 93.0% | 89.0%, 96.9% | 88.7%, 96.8% |
| Capsules-tablets (95% CI) | 3.7% (-8.2%, 15.7%) | | -0.2% (-10.6%, 10.2%) | |
| **Clinical signs** | Visit 2 | | Visit 3 | |
| Number of subjects with available data | 192 | 185 | 185 | 180 |
| Number of responders (n (%)) | 186 (96.9%) | 182 (98.4%) | 183 (98.9%) | 171 (95.0%) |
| 95% CI | 94.2%, 99.6% | 96.3%, 100.5% | 97.2%, 100.7% | 91.5%, 98.5% |
| Capsules-tablets (95% CI) | 1.5% (-6.6%, 9.6%) | | -3.9% (-12.3%, 4.5%) | |
| **Mycological cure** | Visit 2 | | Visit 3 | |
| Subjects with available data (%) | 192 | 184 | 185 | 178 |
| Number of responders, n (%) | 149 (77.6%) | 149 (81.0%) | 150 (81.1%) | 138 (77.5%) |
| 95% CI | 71.4%, 83.8% | 75.0%, 86.9% | 75.2%, 87.0% | 71.1%, 83.9% |
| Capsules-tablets (95% CI) | 3.4% (-9.9%, 16.6%) | | -3.6% (-17.0%, 9.9%) | |

The clinical signs and symptoms of vaginitis were evaluated by the patients (symptoms) and the investigator (signs). By week 2, the majority of patients were free of itching (91.1% tablet, 93.5% capsule) and burning/irritation (89.1% tablet, 92.4% capsule) and the proportion of patients without symptoms was similar in both groups at visit 3 at 6-8 weeks after treatment. Vaginal erythema, ( the most prominent sign at baseline), had resolved within 2 weeks in most patients (89.1% tablet, 88.1% capsule) and the proportion of women without erythema remained essentially unchanged at weeks 6-8 after treatment (89.6% and 87.0%, respectively). The time course of the other clinical signs was similar and there were no relevant differences between groups. In 90% or more of the subjects, clinical signs were no longer present at visit 2 and cure rates were similar at visit 3. The PP analysis confirmed the results of the ITT analysis.

## .IV.5 Clinical Safety

In the pivotal trial comparing clotrimazole 500 mg soft vaginal capsules (n = 235) and clotrimazole 500 mg vaginal tablets (n = 228) in women with vulvovaginal candidiasis the incidence of adverse events was similar in the capsule (8.1%) and the tablet group (8.3%). No serious adverse events occurred and except from one severe adverse event (vaginal infection considered unrelated to the study medication), all adverse events were of mild to moderate intensity.

Only one adverse event (mild vulvovaginal discomfort) experienced by a woman 4 days after application of the capsule was assessed as related to the study medication by the investigator. The tolerability of vaginal clotrimazole is demonstrated for the newly developed soft vaginal capsule formulation in comparison with the long-term approved vaginal tablet formulation.
Clotrimazole has been available as a non-prescription medicine for 24 years. No major safety concerns have arisen.

Pharmacovigilance System
The marketing authorisation holder (MAH) submitted a summary of the Pharmacovigilance System, including confirmation of 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.

**Risk Management Plan:**
The RMP is acceptable.

Summary of safety concerns:

Important identified risks:
- Hypersensitivity reactions

Important potential risks:
- Risk of exposure of foetus during the first trimester of pregnancy
- Risk of exposure of neonate during lactation
- Risk of misdiagnosis
- Development of resistance
- Risk of accidental ingestion
- Risk of environmental toxicity
- Drug interaction with tacrolimus/sirolimus
- Drug interaction with latex condoms/diaphragms

Missing information: None

Routine risk minimisation activities are considered acceptable. No additional RMM required.

**Periodic Safety Update Report (PSUR)**

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

## IV.6 Discussion on the clinical aspects

In this application for clotrimazole 500 mg soft vaginal capsule & clotrimazole 2% cream cross reference is made to the originator medicinal product clotrimazole 500 mg pessary & clotrimazole 2% cream that is already approved for the treatment of the same indication.

The pharmacology of clotrimazole does not change when the new soft vaginal capsule formulation replaces the vaginal tablet formulation in the originator combination pack, as the active principle remains the same. The non-inferiority of the new formulation compared with the tablet formulation in originator product has been demonstrated in the pivotal clinical bridging trial conducted on behalf of the applicant. No new safety issues were identified in this study.

The efficacy of clotrimazole in the treatment of vulvovaginal mycosis has been extensively studied in non-pregnant women and to a lesser extent in pregnant women. The mycological cure rates achieved with clotrimazole in women with vaginal mycosis exceed 80% in the majority of studies. The efficacy and safety of combined clotrimazole treatment with intravaginal formulations (cream or tablet) and external treatment of the anogenital region has been investigated in more than 30 clinical trials and is supported by post-marketing experience.

The results of the pivotal clinical study conducted by the applicant supports the therapeutic equivalence of different clotrimazole formulations (500mg tablet and capsule) for intravaginal use.

The efficacy of clotrimazole vaginal capsule formulation in combination with the already well-established 2% cream are considered to be equally effective to the currently licensed Canesten Combi **(**vaginal tablet formulation and 2% cream).

## V OVERALL CONCLUSIONS

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted, considered that Canesten Soft Vaginal Capsule Combi demonstrated adequate evidence of efficacy for the approved indications as well as a satisfactory risk/benefit profile and therefore have granted a marketing authorisation.

## VI REVISION DATE

## VII UPDATES

**UPDATE**

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 |
|---|---|---|---|---|