IPAR

Public Assessment Report for a

Medicinal Product for Human Use

Scientific discussion

Canesten HC Cream
CLOTRIMAZOLE & HYDROCORTISONE
PA1410/040/002

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 HC 1% w/w + 1% w/w Cream from Bayer Limited on 29th June 2018. The topical treatment of skin infections due to superficial dermatophytes, yeasts, moulds and other fungi sensitive to clotrimazole where co-existing symptoms of inflammation, e.g. itching, require rapid relief.

This application for a marketing authorisation was submitted as a line extension to the existing Canesten HC Cream - PA 1410/040/002, with the legal basis, Article 8(3) of Directive 2001/83/EC.
This product is subject to medical prescription which may be renewed (B) 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 HC Cream
Name(s) of the active substance(s) (INN)	CLOTRIMAZOLE & HYDROCORTISONE
Pharmacotherapeutic classification (ATC code)	D01AC02
Pharmaceutical form and strength(s)	1.0 %w/w
Marketing Authorisation Number(s) in Ireland (PA)	PA1410/040/002
Marketing Authorisation Holder	Bayer Limited

II QUALITY ASPECTS

II.1. Introduction

This application is for Canesten HC 1% w/w + 1% w/w Cream.

II.2 Drug substance

The active substances are clotrimazole and hydrocortisone acetate, established active substances described in the European Pharmacopoeia, and are manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specifications are considered adequate to control the quality and meet current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification have been provided.

II.3 Medicinal product

P.1 Composition

The products contains clotrimazole 1g/100g and hydrocortisone (as acetate) 1g/100g,

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 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 a suitably qualified manufacturing site.

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 dosage form, 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 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./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 HC 1% w/w + 1% w/w Cream.

III NON-CLINICAL ASPECTS

III.1 Introduction

This active substances are essentially the same as that present in Canesten HC cream PA 1410/40/1 on the European market. No new preclinical data have been submitted.
The applicant provided a non-clinical expert report (non-clinical overview) which was written by an appropriately qualified person. The expert report was considered appropriate as it provided a detailed review of the relevant non clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

See clinical section

III.3 Pharmacokinetics

See clinical section

III.4 Toxicology

No new non clinical data were submitted and are not required as the pharmacokinetics, pharmacodynamics and toxicology of clotrimazole and hydrocortisone acetate are well known.

III.5 Ecotoxicity/environmental risk assessment

As the product is intended for substitution of the original product on our market, no increased environmental burden is anticipated. Therefore the MAH’s justification for not submitted an environmental risk assessment report is accepted.

III.6 Conclusion on the non-clinical aspects

There are no objections from a non-clinical perspective.

IV CLINICAL ASPECTS

CLINICAL ASPECTS

IV.1 Introduction

The application is based on bibliographic literature only. The marketing authorisation holder (MAH) submitted their application as a line extension replacement by a different salt/ester, complex/derivative (same therapeutic moiety) to Canesten HC Cream PA 1410/40/1.

The composition of the new Canesten HC cream has slightly changed as hydrocortisone is being replaced with hydrocortisone acetate (see quality section above).

Considering that the line extension to Canesten HC cream PA 1410/40/1 is based on the existing fixed combination and on the recognised scientific principle of using combination treatment in the intended indications, the documentation focuses on the assessment of the exchanges of hydrocortisone alcohol versus hydrocortisone acetate as well as the slight increase of benzyl alcohol (excipient) in Clotrimazole / Hydrocortisone acetate 1% / 1.12% Cream.

Both active Clotrimazole and Hydrocortisone are well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the national procedure is in accordance with that accepted for the originator reference product Canesten HC cream PA 1410/40/1 marketed by MAH.

IV.2 Pharmacokinetics

No biopharmaceutical studies have been conducted with the original or Clotrimazole / Hydrocortisone acetate 1% / 1.12% Cream. The pharmacokinetics of topical clotrimazole has been adequately studied in humans.

Clotrimazole:
Pharmacokinetic investigations after dermal application have shown that clotrimazole is practically not absorbed from intact or inflamed skin into the human blood circulation. The resulting peak serum concentrations of clotrimazole were below the detection limit of 0.01 microg/ml, reflecting that clotrimazole applied topically does not lead to measurable systemic effects or side effects. No clinically relevant changes in the pharmacokinetics/pharmacology of clotrimazole can be expected.

Hydrocortisone:
Dermal absorption of hydrocortisone depends on the thickness and condition of the skin. In healthy skin no systemic effects of corticoids have been observed after local application.

However, in the case of inflamed or damaged skin, cutaneous absorption may be increased depending on the site of application, use of occlusive dressings, the degree of skin damage, and size of the treated area. Systemic effects cannot be ruled out under such conditions.

An increase in the skin temperature or moisture content, e.g. in skin folds or under an occlusive dressing, also promotes absorption. In infants and small children the epidermal "barrier" is still poorly developed, which facilitates transcutaneous uptake of drugs. The occurrence of systemic effects depends partly on the dose and, to a much greater extent, on the duration of treatment.

More than 90% of the hydrocortisone absorbed is bound to plasma proteins. Hydrocortisone is metabolised in the liver and tissues, and the metabolites are excreted with urine. The biological half-life is approximately 100 minutes.

No relevant absorption of hydrocortisone is expected after its use for a short period on limited skin inflamed areas.

IV.3 Pharmacodynamics

Mechanism of Action

Clotrimazole
Clotrimazole acts against fungi by inhibiting ergosterol synthesis. Inhibition of ergosterol synthesis leads to structural and functional impairment of the fungal cytoplasmic membrane.

Clotrimazole has a broad antimycotic spectrum of action in vitro and in vivo, which includes dermatophytes, yeasts, moulds, etc.

Under appropriate test conditions, the MIC values for these types of fungi are in the region of less than 0.062 –-8.0) microg/ml substrate. The mode of action of clotrimazole is fungistatic or fungicidal depending on the concentration of clotrimazole at the site of infection. In vitro activity is limited to proliferating fungal elements; fungal spores are only slightly sensitive.

In addition to its antimycotic action, clotrimazole also acts on gram-positive microorganisms (streptococci/staphylococci/Gardnerella vaginalis) and gram-negative microorganisms (Bacteroides/). It has no effect on lactobacilli.

In vitro, clotrimazole inhibits the multiplication of Corynebacteria and gram-positive cocci – with the exception of enterococci – in concentrations of 0.5 – 10 microg/ml substrate.Primary resistant variants of sensitive fungal species are very rare; the development of secondary resistance by sensitive fungi has so far only been observed in very isolated cases under therapeutic conditions.

Hydrocortisone
Hydrocortisone is a weak corticosteroid with both glucocorticoid and to a lesser extent mineralocorticoid activity. As the active ingredient in a topical cream it exerts anti-inflammatory, antipruritic, anti-exudative and anti-allergic effects.

Hydrocortisone exerts an anti-inflammatory, immunosuppressive, antimitotic (antiproliferative), antiallergic, antipruriginous and vasoconstrictive effect on the skin. Thus, in addition to the elimination of inflammation and pruritis, a normalisation of keratinisation, inhibition of excess fibroblast activity and epidermopoiesis, degradation of pathological metabolic products and inhibition of acantholysis are achieved. Pharmacokinetic Properties areas.

IV.4 Clinical Efficacy

The documentation is based on bibliographic literature only. The marketing authorisation holder (MAH) submitted their application as a line extension to Canesten HC Cream PA 1410/40/1.

The composition of the new Canesten HC cream has slightly changed as hydrocortisone is being replaced with hydrocortisone acetate (see quality section above).

Considering that the line extension is based on the existing fixed combination and on the recognised scientific principle of using combination treatment in the intended indications, the documentation focused on the assessment of the exchanges of hydrocortisone alcohol versus hydrocortisone acetate as well as the slight increase of benzyl alcohol (excipient) in Clotrimazole / Hydrocortisone acetate 1% / 1.12% Cream.

Hydrocortisone alcohol and acetate are equipotent, low-potency corticosteroids and are regarded as interchangeable for topical therapy of a variety of dermatoses. The rationale for the change of hydrocortisone alcohol exchanged by hydrocortisone acetate was for stability reasons.

Local bioavailability/activity of hydrocortisone alcohol and acetate is considered to be similar if applied in a similar or identical vehicle.

The difference in benzyl alcohol (excipient) content was also adequately justified.

No new clinical pharmacology data have been submitted for this application. The clinical pharmacology of clotrimazole and hydrocortisone acetate is well known and has been adequately summarised in the clinical overview provided by the MAH.

The efficacy of clotrimazole and hydrocortisone acetate is well known. No new efficacy data has been submitted or is required to support this application. The MAH has provided sufficient justification in relation to the efficacy and no difference in efficacy is anticipated

IV.5 Clinical Safety

No new safety data has been submitted with this application and are not required. As the active constituents clotrimazole and hydrocortisone acetate have well established safety profiles. Both hydrocortisone alcohol and acetate are low-potency corticosteroids.

Hydrocortisone alcohol and acetate are used by millions of patients for the topical treatment of a variety of dermatoses and the risk of systemic effects seems to be uniformly low despite the differences in the galenic formulations (creams, ointments, or lotions) and vehicles of the approved products.

No clinically relevant change of the safety profile, either in terms of local tolerability or the risk of systemic adverse effects, is expected from the exchange of hydrocortisone alcohol by its acetate in an equimolar concentration.

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

Suitable justification has been provided for not submitting a risk management plan for this line extension.

PSUR cycle will continue as per current Canesten HC cream PA 1410/40/1

IV.6 Conclusion on the clinical aspects

There are no objections from a clinical perspective

V OVERALL CONCLUSIONS

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Canesten HC cream is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Quality
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 HC 1% w/w + 1% w/w Cream.

Non Clinical
No new non clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of both active constituentrs (clotrimazole and hydrocortisone acetate) are well known no additional non clinical studies were required.

Clinical

Efficacy
No new efficacy data was submitted for this application

Safety
No new safety data was submitted for this application which is acceptable as both active constituents are well known. The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

Product information
No changes to the product information SmPC patients leaflet or labelling were proposed, there it will remain the same as the current Canesten HC cream PA 1410/40/1.

Benefit/risk
Overall the benefit risk is considered positive and a marketing authorisation was granted.

VI REVISION DATE

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