CANESTEN HC CREAM
(clotrimazole and hydrocortisone acetate)

PL 00010/0643

UKPAR

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The Medicines and Healthcare products Regulatory Agency (MHRA) granted Bayer plc (trading as Bayer plc, Consumer Care Division) a Marketing Authorisation for the medicinal product Canesten HC Cream (PL 00010/0643) on 19 April 2013. This medicine is only available on prescription from your doctor and is used to treat the following conditions:

- Fungal skin infections when there are additional symptoms of inflammation (such as swelling, redness and itching). Canesten HC treats the fungal skin infection and reduces the swelling and itching caused by it.
- Infection and irritation of the vulva or end of the penis (glans) caused by thrush.
- Nappy rash and fungal infection of the breast fold (intertrigo), as well as infections such as ringworm and athlete’s foot.

The active substances in Canesten HC Cream are clotrimazole and hydrocortisone acetate. Clotrimazole belongs to a group of medicines called imidazoles, which destroy the fungi and some bacteria that cause skin infections. Hydrocortisone acetate is a mild steroid which reduces swelling, redness and itching associated with inflammation of the skin.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using Canesten HC Cream outweigh the risks and a Marketing Authorisation was granted.
Canesten HC Cream  
(clotrimazole and hydrocortisone acetate)  

PL 00010/0643

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Bayer plc (trading as Bayer plc, Consumer Care Division) a Marketing Authorisation for the medicinal product Canesten HC Cream (PL 00010/0643) on 19 April 2013. This product is a prescription-only medicine (POM) indicated for the treatment of the following skin infections where co-existing symptoms of inflammation, e.g. itching, require rapid relief:

- All dermatomycoses due to dermatophytes (e.g. Trichophyton species), moulds and other fungi.
- All dermatomycoses due to yeasts (Candida species).
- Skin diseases showing secondary infection with these fungi.
- The treatment of nappy rash where infection due to Candida albicans is present. Candidal vulvitis, candidal balanitis and candidal intertrigo.

Canesten HC Cream contains the active ingredients hydrocortisone acetate and clotrimazole. Clotrimazole, a synthetic imidazole derivative, is a broad spectrum antifungal. It also exhibits activity against *Trichomonas*, staphylococci, streptococci and *Bacteroides*. It has no effect on lactobacilli. Hydrocortisone acetate is one of the oldest corticosteroids used topically, for the treatment of inflammatory skin conditions such as pruritus and oedema, and is a standard low potency corticosteroid.

This application was submitted under Article 10(b) of Directive 2001/83/EC (as amended), applicable for a fixed combination product of known active substances. The application for Canesten HC Cream (PL 00010/0643) is a change to the applicant’s existing (originator) Marketing Authorisation for Canesten HC Cream (PL 00010/0120) granted in the UK on 14 February 1984. Canesten HC Cream (PL 00010/0643) contains 1% w/w clotrimazole and 1.12% w/w hydrocortisone acetate (equivalent to 1% hydrocortisone); the only modification compared to the originator product is the replacement of the hydrocortisone (alcohol) component by the acetate (an ester of hydrocortisone). Hydrocortisone and hydrocortisone acetate are considered interchangeable in clinical use and the qualitative and quantitative composition of the vehicle in the medicinal product remains essentially unchanged. The second active, clotrimazole 1% is qualitatively and quantitatively identical to that in the originator product. Bayer plc has committed to stop marketing PL 00010/0120 following the launch of PL 00010/0643 on the market.

No new non-clinical or clinical studies were performed or required. The submitted dossier refers to the originator documentation and the clinical overview includes the current state of knowledge in relation to the active substances hydrocortisone acetate and clotrimazole, both singly and in combination. Additional bibliographic clinical data to support the well established comparable safety and efficacy of hydrocortisone acetate compared to hydrocortisone alcohol is also provided.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Canesten HC Cream outweigh the risks and a Marketing Authorisation was granted.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE – CLOTRIMAZOLE
INN: Clotrimazole
Chemical Name: 1-(2-chloro-α,α-diphenyl-benzyl)imidazole
1-(o-chloro-α,α-diphenyl-benzyl)imidazole
1-(2-chlorotrityl)imidazole
1-[(2-chlorophenyl)-diphenylmethyl]-1H-imidazole
Molecular Formula: C_{22}H_{17}ClN_{2}

Clotrimazole is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance clotrimazole are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

ACTIVE SUBSTANCE – HYDROCORTISONE ACETATE
INN: Hydrocortisone acetate
Chemical Name: 11β,17-Dihydroxy-3,20-dioxopregn-4-en-21-yl acetate
Molecular Formula: C_{23}H_{32}O_{6}

Hydrocortisone acetate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance hydrocortisone acetate are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

DRUG PRODUCT
Other Ingredients
Other ingredients consist of the pharmaceutical excipients namely benzyl alcohol, cetostearyl alcohol, medium chain triglycerides, triceteareth-4-phosphate, purified water, sodium hydroxide and hydrochloric acid. Appropriate justification for the inclusion of each excipient has been provided.
All excipients comply with their respective European Pharmacopoeia monographs, except triceteareth-4-phosphate which is controlled to a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

None of the excipients contains materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**
The objective of the development programme was to formulate a safe, efficacious, stable oil-in-water (o/w) emulsion for topical administration containing 1%w/w clotrimazole and 1.12% w/w hydrocortisone acetate (equivalent to 1% hydrocortisone).

Suitable pharmaceutical development data have been provided for this application.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Based on pilot and production-scale batches, the manufacturing process has been validated and has shown satisfactory results. The Marketing Authorisation holder (MAH) has committed to performing process validation on future production-scale batches.

**Control of Finished Product**
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**
The cream is packaged in aluminium tubes with internal lacquer coating and high-density polyethylene (HDPE) screw-on caps. These are packed into cardboard cartons with Patient Information Leaflets in pack sizes of 5 g sample pack, 15 g and 30 g. Not all pack sizes are marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months for the unopened tube and 6 months for the opened tube, with the storage conditions ‘Do not store above 25°C.’

Suitable post approval stability commitments have been provided to continue stability studies on batches of finished product.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SmPC, PIL and labelling are satisfactory from a pharmaceutical perspective. User testing of the package leaflet has been accepted, based on a bridging report provided by the applicant that makes reference to the user test report for the PIL for Canesten Hydrocortisone (PL 00010/0216; Bayer plc, UK).

**MAA (Marketing Authorisation Application) Form**
The MAA form is satisfactory from a pharmaceutical perspective.
Expert Report (Quality Overall Summary)
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
As the pharmacodynamic, pharmacokinetic and toxicological properties of clotrimazole and hydrocortisone acetate are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT (NON-CLINICAL OVERVIEW)
The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

ENVIRONMENTAL RISK ASSESSMENT
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this product is intended for substitution of a product that is already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of a Marketing Authorisation is recommended.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
No new clinical pharmacology data have been submitted or required for this application. The clinical pharmacology of clotrimazole and hydrocortisone acetate is well known and is adequately summarised in the clinical overview.

EFFICACY
The efficacy of clotrimazole and hydrocortisone acetate is well-known. No new efficacy data have been submitted or required for this application.

SAFETY
No new safety data have been submitted with this application or none are required. No new or unexpected safety concerns arose from this application. As the active ingredients, clotrimazole and hydrocortisone acetate have well-established safety profiles and an acceptable level of safety in the proposed indications.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant 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.

Suitable justification has been provided for not submitting a Risk Management Plan for this product.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPC, PIL and labelling are satisfactory from a clinical perspective. The SmPC is consistent with that for the MAH’s originator product Canesten HC Cream (PL 00010/0120). The PIL is consistent with the details in the SmPC and in line with the current guidelines. The labelling is in line with current guidance.

CLINICAL EXPERT REPORT (CLINICAL OVERVIEW)
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

CONCLUSION
The grant of a Marketing Authorisation is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Canesten HC Cream 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
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of clotrimazole and hydrocortisone acetate are well-known, no additional data were required.

EFFICACY
No new data were submitted or required for this application.

SAFETY
No new data were submitted or for this application, as the safety profiles of clotrimazole and hydrocortisone acetate are well-known.

PRODUCT LITERATURE
The SmPC, PIL and labelling are acceptable. The SmPC is consistent with that for MAH’s originator product Canesten HC Cream (PL 00010/0120). The PIL is consistent with the details in the SmPC and in line with the current guidelines. The labelling is in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with clotrimazole and hydrocortisone acetate is considered to have demonstrated the therapeutic value of the product. The benefit/risk balance is, therefore, considered to be positive.
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STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the Marketing Authorisation application on 29 December 2011.
2. Following standard checks and communication with the applicant the MHRA considered the application valid on 17 April 2012.
3. Following assessment of the application the MHRA requested further information relating to the quality dossier on 14 June 2012.
4. The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 12 December 2012.
5. The application was granted on 19 April 2013.
STEPS TAKEN AFTER INITIAL PROCEDURE – SUMMARY

The following table lists a non-safety update to the Marketing Authorisation for this product that have been approved by the MHRA since the product was first licensed.

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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<td>26/04/2013</td>
<td>Type IA</td>
<td>To register the replacement of the Detailed Description of Pharmacovigilance System (DDPS) by the introduction of the Summary of the Pharmacovigilance System Master File. Consequently, the details of the Qualified Person for Pharmacovigilance have been changed.</td>
<td>Approved 16/05/2013</td>
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SUMMARY OF PRODUCT CHARACTERISTICS

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