LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Hydrokortison CCS
(hydrocortisone)

SE/H/321/01/E01

This module reflects the scientific discussion for the approval of Hydrokortison CCS. The procedure was finalised on 2015-05-28. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

The application for Hydrokortison CCS, 1%, cream, is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The applicant, CCS Healthcare AB, applies for a marketing authorisation in DK, FI, IS through this repeat use procedure with Sweden acting as reference member state (RMS). The product was first nationally approved in Sweden and then approved through a Mutual Recognition Procedure with NO as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Uniderm, 1%, cream, authorised in SE since 1980, with Schering-Plouge Europe as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological effects of glucokorticoids including hydrocortisone are considered well known and no formal pharmaco-toxicological assessment has been made. From a non-clinical point of view, Hydrocortison CCS, 1%, cream is recommended for market authorisation.

Environmental Risk Assessment (ERA)

Since Hydrokortison CCS 1% cream is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

IV. CLINICAL ASPECTS

Hydrocortisone 1% has been used in the treatment of eczema of varying genesis for decades, also with OTC status. Hence, the clinical efficacy is considered well documented. Adverse effects are mostly mild involving local reactions in the skin. The systemic absorption is negligible and systemic adverse events are unlikely with topical administration of low concentrations of hydrocortisone. Considering the large amount of individuals exposed to hydrocortisone 1% and the favourable benefit/risk profile, the product is recommended for market authorisation.

The absence of pharmacokinetic bioequivalence studies is acceptable since the product is a locally applied, locally acting product.

For locally applied, locally acting products, the Note for Guidance on the Clinical Requirements for Locally Applied, Locally Acting Products Containing Known Constituents (CPMP/EWP/239/95 final) and the “Questions and answer on guideline title: Clinical investigation of corticosteroids intended for use on the skin (CHMP/EWP/21441/2006)”are applicable. These state that in order to demonstrate therapeutic equivalence clinical trials are in principle necessary, but other models may be used or developed. For topical corticosteroids (TCS), the vasoconstriction assay (VCA) is considered a valid model to establish pharmacodynamic equivalence between two TCS products.

The lack of a pharmacodynamic vasoconstriction study for Hydrokortison CCS 1% cream may be regarded as a deficiency. However, it should be acknowledged that the product was first approved in Sweden in the early 1990s, and at that time these guidelines were not in place. From a quality perspective, the composition of Hydrokortison CCS, 1%, cream is identical with the original product Uniderm, 1%, cream (Schering Plough, approved in Sweden 1980), with the exception of the preservative agent. The efficacy and safety profiles of topically applied hydrocortisone preparations have been established through over 40 years of marketing experience and Hydrokortison CCS 1% cream has been approved in Sweden since 1990. Hence, the lack of a pharmacodynamic vasoconstriction study for Hydrokortison CCS 1% cream may be regarded mainly as a formal deficiency with no impact for the benefit-risk profile for the product. However, during discussions between the RMS and the CMS during the MR procedure, it was concluded that a study should be performed post-approval, to confirm the clinical efficacy of Hydrokortison CCS 1% cream, preferably using the VCA methodology.

IV.1 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Hydrokortison CCS. The proposed pharmacovigilance activities and proposed risk minimisation activities by safety concern are outlined below:

Safety concern	**Important identified risk:** **Adrenal suppression**
Objective(s) of the risk minimisation measures	The product labelling (SmPC and package leaflet) is the primary tool for dissemination of risk and safety information for Hydrokortison CCS 1 % cream and Hydrokortison CCS 1% ointment to healthcare providers. The labelling communicates all important risk and safety information. As a part of routine risk minimisation activity, section 5.2 "Pharmacokinetic properties" of the product information, adequately address this safety concern.
Routine risk minimisation measures	Text in SmPC: *Pharmacokinetic properties (section 5.2):* Glucocorticoids have the ability to penetrate stratum corneum of the epidermis and affect the deeper cell layers. Usually only a small proportion of the dose is absorbed, and it is thus not expected to affect the hormonal balance. The systemic effect of glucocorticoids can occur in the event of increased absorption, e.g. when applied on large inflamed areas of skin, or on skin of which the stratum corneum of the epidermis is damaged. Occlusive bandages increase absorption.
Additional risk minimisation measure(s)	None Proposed

Safety concern	**Important identified risk:** **Contact dermatitis**
Objective(s) of the risk minimisation measures	The product labelling (SmPC and package leaflet) is the primary tool for dissemination of risk and safety information for Hydrokortison CCS 1 % cream and Hydrokortison CCS 1% ointment to healthcare providers. The labelling communicates all important risk and safety information. As a part of routine risk minimisation activity, section 4.3 "Contraindications" and section 4.8 "Undesirable effects" of the product information, adequately address this safety concern.
Routine risk minimisation measures	Text in SmPC: *Contraindications (section 4.3):* Hypersensitivity to hydrocortisone or to any of the excipients. *Undesirable effects (section 4.8):* Skin and subcutaneous tissue disorder: Uncommon (>1/1,000, <1/100):Irritation, conctact dermatitis Cases of allergic contact dermatitis (hydrocortisone) have been reported.
Additional risk minimisation measure(s)	None Proposed

Safety concern	**Important potential risk:** **Ocular complications**
Objective(s) of the risk minimisation measures	The product labelling (SmPC and package leaflet) is the primary tool for dissemination of risk and safety information for Hydrokortison CCS 1 % cream and Hydrokortison CCS 1% ointment to healthcare providers. The labelling communicates all important risk and safety information. As a part of routine risk minimisation activity, section 4.4 "Special warnings and special precautions for use" of the product information, adequately address this safety concern.
Routine risk minimisation measures	Text in SmPC: *Special warnings and special precautions for use (section 4.4):* Contact with the conjunctiva must be avoided.
Additional risk minimisation measure(s)	None Proposed

The RMP was found acceptable.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Hydrocortison CCS ointment, SE/H/321/02. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Hydrokortison CCS, 1%, cream, is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

- A post-approval study to demonstrate the clinical efficacy of Hydrokortison CCS 1% cream, preferably using the VCA-methodology. The study will commence within a timeframe of 12 months after finalized procedure and the new data will be included in the product dossier with a type II variation. Since there can be practical problems to perform a conventional VCA therapeutic equivalence study, e.g. if the reference product is no longer available on the market, the study design may need to be adopted accordingly.

- Update SmPC, PL and labelling in line with section 4.2 – 4.4 in line with the SmPC approved for SE/H/0619/001/MR and according to other comment made by FI, DK and IS during the procedure. The changes will be implemented with a variation submitted within 2 months after finalized procedure.

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC
N/A

VII. APPROVAL

The Mutual recognition procedure for Hydrokortison CCS, 1%, cream, was positively finalised on 2015-05-28.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se