LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Canoderm cream 5 %
(Urea)

SE/H/556/01

This module reflects the scientific discussion for the approval of Canoderm 5% creme. The procedure was finalised at 2006-02-27. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

ACO HUD AB has applied for a MR procedure with SE as RMS and DK, FI and NO as CMS. The application is bibliographical, according to Article 10.1(a)(ii) of Directive 2001/83/EC.

Canoderm cream was approved for Marketing Authorisation in Sweden 1997-12-19 (renewal date 2002-12-19). Since approval some variations have been applied for and approved. The product is indicated for treatment of dry skin conditions of different origin.

II. QUALITY ASPECTS

II.1 Introduction

Canoderm cream is presented in form of an oil in water emulsion containing urea 50 mg/g active ingredient.
The excipients are fractionated coconut oil, emulsifying wax, hydrogenated canola oil, propylene glycol, carbomer, dimethicone, hard paraffin, glycerol polymetacrylate, propyl parahydroxybenzoate (E 216), methyl parahydroxybenzoate (E 218), sodium lactate solution, lactic acid, glyceryl stearate, polyoxyethylene stearate and purified water.

The cream is filled in white plastic tubes (polyethylene) or white plastic jars (polypropylene) with pump and refill jars to plastic jars with pump.

II.2 Drug Substance

Urea has a monograph in the Ph Eur. Urea has a long and safe historic use, the chemical structure and the stability of urea is well documented in the literature.

Urea is a white, crystalline powder of transparent crystals very soluble in water, soluble in alcohol, practically insoluble in methylene chloride. Urea is slightly hygroscopic. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.
The active substance specification includes relevant tests and the limits for impurities/ degradation products have been justified. The analytical methods applied are suitably described and validated.
Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Canoderm 5% cream is formulated using 15 excipients. The majority of them are described in the current Ph Eur. Fractionated coconut oil is tested according to BP and emulsifying wax is tested according to USP/NF. Three of the excipients, hydrogenated canola oil, the mixture glyceryl polymethacrylate-propylene glycol-water and the mixture glyceryl stearate-polyoxyethylene stearate are controlled according to acceptable in house specifications.

No raw materials used in the product are of human or animal origin.

The product development has taken into consideration the physico-chemical characteristics of the active substance and of the excipients. The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.
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 under ICH conditions have been performed and the presented data support the shelf-life of 2 years, claimed in the SPC when stored below 25ºC in both tubes and jars.
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III. NON-CLINICAL ASPECTS

Urea is considered well known from a pharmacodynamic, pharmacokinetic and toxicological point of view. The excipients of Canoderm cream are present in other topical formulation on the Swedish market or in cosmetic products manufactured by ACO Hud AB. Hence, from a non-clinical perspective, no safety concerns for humans can be anticipated with clinical use of Canoderm cream.

IV. CLINICAL ASPECTS

IV.1 Clinical efficacy

Three studies of different aspects of Canoderm 5% cream involving healthy volunteers or patients have been submitted. One of these is an investigation of safety aspects assessing potential allergenicity and/or local irritation of Canoderm 5% cream in healthy volunteers. The other two studies are comparative investigations of the clinical efficacy of Canoderm 5% cream versus Fenuril cream in patients with atopic dermatitis and hand eczema respectively.

Efficacy
48 patients (25 used Canoderm, 23 Fenuril) finished the study in atopic dermatitis and are included in analysis of results. The study duration was 30 days and the cream was applied twice daily. Mean and median DASI-scores (*d*ry skin *a*rea and *s*everity *i*ndex) decreased during treatment but there were no statistically significant differences between treatment groups. The patients themselves evaluated the effect on dryness and irritation on a VAS scale. Some improvement was noted. No statistically significant difference was found between treatments. Skin barrier function was measured as transepidermal water loss (TEWL) by means of an Evaporimeter and skin capacitance was measured by a Corneometer. No statistically significant difference could be observed between or within the patient groups during the study. Patients on Fenuril used corticosteroids sometimes in 43%, never in 17%, as compared to 68 and 24% for patients on Canoderm. This could be taken as an indication that the groups treated were not equal in severity of disease. There was no difference in the median values for DASI-scores initially to support this, however.
The second study with a duration of 30 days and comparing the moisturizing effect of Canoderm 5% cream to that of Fenuril cream included 78 patients with hand eczema (40 used Canoderm, 38 Fenuril) in analysis of results. After 30 days of treatment the total disease activity score had changed from 9,0 to 8,0 in the Canoderm group, from 9,0 to 9,5 in the Fenuril group. The patients themselves evaluated the effect of treatment on dryness and irritation on a VAS scale. No statistically significant difference was found between treatments. The primary efficacy variable chosen for the clinical studies is adequate and supported by adequate evaluations made by the patients. Conclusions for the objective measurements of skin barrier function and skin capacitance were the same as in study 1.

IV.2 Clinical safety

The vehicle of Canoderm 5% cream is not part of any other moisturizer approved as a medicinal product. One of the ingredients in the vehicle is canola oil which in itself has been found to alleviate surfactant-induced irritation. Among other ingredients included is acetylated lanolin alcohol which may cause contact allergy.
A study with the objective to determine skin irritation and contact sensitisation potential of three skin creams and one skin lotion has been submitted. Dermatological adverse events of known type, weak to moderate itching, stinging and dryness were seen in 10-20% of the patients in both treatment groups in the clincial studies. None of them was serious. In no case did it contribute to withdrawal from Canoderm treatment. Systemic adverse events were considered not to be related to the treatment which seems adequate. Results from the study performed to determine skin irritation and contact sensitisation potential of Canoderm point to a low risk. The drug can thus be considered safe.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has not been performed. The applicant has made a commitment to perform user testing during 2006.

The benefit of Canoderm 5% cream is greater than the risk of adverse events.
However, the two clinical studies taken together do not lend enough support to point out efficacy for Canoderm 5% cream in a more specified condition than dry skin of different origin. The safety study and evaluation of adverse events in the clinical studies show it to be a safe product. The limited size of the submitted documentation concerning clinical efficacy and the lack of placebo control in the studies makes it difficult to draw conclusions about therapeutical equivalence. Tolerance is judged to be the most important parameter to be evaluated. The two clinical studies along with the tolerance study make up a large enough material to perform an evaluation of this.