LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Curemid
(urea)

SE/H/2136/01/MR

This module reflects the scientific discussion for the approval of Curemid. The procedure was finalised on 2021-09-03. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Curemid, 50 mg/g, Cream.

The active substance is urea. A comprehensive description of the indication and posology is given in the SmPC.

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

The application for Curemid, 50 mg/g, cream is submitted according to Article 10a of Directive 2001/83/EC. For an application according to Article 10a, WEU, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use for the claimed therapeutic indication within the Union for at least ten years, with recognised efficacy and an acceptable level of safety.

The applicant, Avia Pharma AB, applies for a marketing authorisation in NO through this mutual recognition procedure with Sweden acting as reference member state (RMS). The product was initially approved in Sweden/RMS in 2011, through the National Procedure.

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 pharmacology, pharmacokinetics and toxicology data provided to support the present Application for Curemid Cream 5% are based on published scientific literature. While limited in scope, the non-clinical data provided are considered sufficient to support this application. Urea is an endogenous product of protein and amino acid catabolism, and the bulk of human exposure to urea results from urea ingestion through plant food and meat. The estimated human exposure level for urea can probably vary widely depending on the food consumed.

Urea contributes to the preservation of healthy skin hydration levels. Its dermatological effects are considered well-established and involves contributing to the hydration of the stratum corneum. Urea-containing products have for long been used in the treatment of different dry skin conditions.

Toxicity testing of urea is limited, and meaningful NOAELs from animal studies are difficult to find. However, based on toxicity studies performed in several species with different routes of administration, NOAELs are likely in the order of g/kg body weight/day. Accordingly, no systemic safety concerns are expected after dermal exposure from a non-clinical perspective.

Urea is a biomolecule present in most if not all species and is a natural part of the environment. Based on the common presence in the environment, the product is unlikely to alter the concentration or distribution of urea in the environment, why no increased environmental risks are anticipated.

IV. CLINICAL ASPECTS

Pharmacokinetics
No pharmacokinetic studies have been performed for this product. Curemid is a product for topical application. Hence, conventional pharmacokinetic bioequivalence studies are not relevant due to low systemic exposure to urea.

Pharmacodynamics/Clinical efficacy/Clinical safety

Pharmacodynamics
Urea/carbamide is considered a well-known constituent of moisturizing creams. The mode of action of urea/carbamide in Curemid 5% cream is the same as in Canoderm 5% cream. The water-binding and barrier- strengthening ability of the creams contributes to normalization of dry skin.

Clinical efficacy
The efficacy of urea/carbamide in the treatment of dry skin of different origin has been descibed extensively in the literature and is considered well known. Curemid can be used for treatment of dry skin of various genesis. Review of scientific literaure shows that dry skin, atopic dermatitis, ichthyosis, dry chapped hands and psoriasis benefit from topical treament with urea/carbamide-containing formulations.

Patients should be encouraged to use moisturizing creams when needed preferably several times a day especially after contact with water.

Clinical safety
The active ingredient urea is a normal occurring metabolite in the body and topical treatment will not induce any systemic toxicity. The safety profile of urea/carbamide 5% when used in moisturizing creams is considered well known.

The labelling of clinical safety in the SmPC of Curemid is considered to adequately reflect the safety data available. There are no reasons to restrict the use during pregnancy and lactation. There is no

potential of the medicinal product to affect ability to drive or operate heavy machinery. Curemid may cause temporary smarting or stinging sensations in the skin, especially in the facial area. Hypersensitivity to other ingredients in the vehicle may occur.

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, characterize, prevent or minimize risks relating to Curemid.

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 0.1 signed 12th May 2020 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the MPA;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimization) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Urea/carbamide containing formulations have been authorised for treatment of dry skin in Sweden and in various other countries within the EU for decades and have a recognised efficacy profile and acceptable level of safety.

The benefit risk assessment of the product is considered positive.

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

N/A

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

N/A

VII. APPROVAL

The mutual recognition procedure for Curemid, 50 mg/g, Cream was positively finalised on 2021-09-03.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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