LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Karbamid Evolan
(urea)

Asp no: 2020-0960

This module reflects the scientific discussion for the approval of Karbamid Evolan. The procedure was finalised on 2022-12-05. 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.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Karbamid Evolan, 50 mg/g, Cutaneous emulsion.

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 Karbamid Evolan, 50 mg/g, cutaneous emulsion, is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The applicant, Evolan Pharma AB applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Canoderm, 50 mg/g, cutaneous emulsion authorised in SE since 1999, with ACO Hud Nordic AB as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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

Pharmacodynamic, pharmacokinetic and toxicological properties of urea are well known. As urea is a widely used, well-known active substance, no further studies are required, and the applicant provides none. Overview based on literature review is, thus, appropriate.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate and is considered sufficient to support the application. There are no objections to approval of Karbamid Evolan from a non-clinical point of view.

Environmental Risk Assessment (ERA)
A justification for not performing an ERA has been submitted. Overall, 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.

IV. CLINICAL ASPECTS

Pharmacokinetics
No bioequivalence study has been submitted. According to Note for Guideline on the Clinical Requirement for Locally Applied, Locally Acting Products Containing Known Constituents (CPMP/EWP/239/95), for locally applied products bioequivalence is generally not a suitable way to show therapeutic equivalence since plasma levels are not relevant for local efficacy, although they may play a role regarding safety.

The applicant submitted justification for not conducting a bioequivalence study. From the pharmacokinetic perspective, a waiver of therapeutic equivalence data may be accepted on quality equivalence alone. For the quality assessment of the product, see section III.1 Quality aspects.

Pharmacodynamics/Clinical efficacy/Clinical safety
Urea is considered a well-known constituent of moisturizing products. The mode of action of urea in Karbamid Evolan is the same as in the reference product Canoderm, 50 mg/g, cutaneous emulsion. The water-binding and barrier-strengthening ability of the creams contributes to normalization of dry skin.

The efficacy of urea in the treatment of dry skin of different origin is considered well known. There are on the Swedish market several moisturizing medicinal products containing urea as active ingredient such as Canoderm® and Fenuril®.

The safety profile of urea 5% when used in moisturizing products is considered well known. The labelling of clinical safety in the SmPC of Karbamid Evolan is considered to adequately reflect the safety data available.

For approval of Karbamid Evolan from a clinical perspective it is essential to show pharmaceutical similarity between the products proposed for marketing, and the reference product chosen by the Applicant. The reason for this is that therapeutic equivalence for moisturizing products is accepted based on quality equivalence alone, since comparative efficacy and safety studies are not possible to perform. The qualitative composition of the test product and the reference product are assessed to be identical, except for the preservatives used. For some of the excipients there is a quantitative difference above 10%, but this is judged acceptable for this kind of emollient cutaneous emulsion. Overall, the product proposed for marketing is considered almost identical to the reference product Canoderm, 50 mg/g, cutaneous emulsion.

Pharmacovigilance system
The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the MPA considers the Summary acceptable.

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 Karbamid Evolan.

Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance Plan

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

Risk minimisation measures
Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 0.1 signed 14th of 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 minimisation) 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

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 Canoderm 5 % cream, SE/H/0556/001/MR, regarding content and Natriumklorid Evolan 500 mg capsules, 5.4.1-2014-5246, regarding layout.
The bridging has been assessed and accepted.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The aim was to develop an essentially similar product to the reference product Canoderm 50 mg/g, cutaneous emulsion. The qualitative composition mimicked the composition of Canoderm, except for the preservatives used. Furthermore, the viscosity and microstructure of the applied product and reference product are similar.

For approval of Karbamid Evolan from a clinical perspective it is essential to show pharmaceutical similarity between the products proposed for marketing, and the reference product chosen by the Applicant. The qualitative composition of the test products and the reference product are assessed to be identical, except for the preservatives used. Overall, the product proposed for marketing is considered almost identical to the reference product Canoderm, 50 mg/g, cutaneous emulsion. From a clinical perspective, the benefit risk of the product is therefore 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

Karbamid Evolan, 50 mg/g, Cutaneous emulsion was approved in the national procedure on 2022-12-05.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

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)

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.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se