LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Canoderm Duo
(propylene glycol, urea)

This module reflects the scientific discussion for the approval of Canoderm Duo. The procedure was finalised at 2025-10-21. 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, the Member States have agreed to grant a marketing authorisation for Canoderm Duo, 50 mg/g + 200 mg/g, Cutaneous emulsion.

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

II. EXECUTIVE SUMMARY

II.1 Rationale for the product

Dry skin disorders are induced by complex interactions between environmental and individual factors and is a common problem both in healthy individuals and in patients with skin diseases. Dry skin might be connected to some inherited disorders relating to the structure and function of the epidermis, e.g. atopic dermatitis (AD), ichthyosis and may also be secondary to other diseases, e.g. diabetes or renal failure.

Although dry skin may occur due to various reasons, it has similar clinical picture and usually appears as a failure of the outermost skin layer, stratum corneum, to retain water. Dry skin is characterized by one or several features: reduced level of natural moisturizing factors and alteration in lipid composition and organization in stratum corneum. This results in lower water content in stratum corneum, increased permeability and other distortions in the skin barrier function, observed for example as increased trans epidermal water loss (TEWL) and less resistance to absorption of noxious substances. The manifestation of dry skin is similar in children and in adults.

Current therapies
Patients are encouraged to use moisturizers several times during the day to strengthen the skin barrier and to reduce the dryness of the skin. The main function of moisturizers is to smoothen the skin surface and to increase its water content i.e., to moisturize and hydrate the skin. The primary target of moisturizers is the outermost layer of the skin, stratum corneum. A 5% urea cream with documented skin barrier strengthening effect was shown to prevent relapse of atopic eczema and increase the eczema free time, indicating the importance of a strengthening effect on the skin in addition to improved skin hydration.

The best moisturizing product for an individual is one that is preferred. Easily applied and rapidly absorbed emulsions with immediate effect are more likely to be perceived as beneficial by the user and their continued use encouraged. The consumer acceptability of Canoderm Duo was tested and scored well on all parameters measured and was rated as good as a 200 mg/g propylene glycol lotion.

In Sweden, only pharmaceutical creams can be included in the reimbursement system. The table below (Table 1) includes the current treatment options registered as medicines in Sweden.

Table 1. Treatments authorised by Swedish Medical Products Agency

Invented name and active substance	**Indication and age groups**
Fenuril (Urea (40 mg/g) + Sodium chloride (40mg/g))	Dry skin. All ages

Canoderm 5% cream (Urea (50mg/g))	Cream: For moisturizing of dry skin of different origin and for prevention of relapse of atopic eczema. All ages Emulsion: dry skin of different origin. All ages
Calmuril (Urea (100 mg/g) + Lactic acid (50 mg/g))	Dry hyperkeratotic skin, ichthyosis, moisturizing during treatment of atopic dermatitis. All ages
Miniderm 20% cream (Glycerol (200mg/g))	Dry skin. All ages
Propyless 200 mg/g cutaneus emulsion (Propylene glycol 200 mg/g))	Dry skin of different origin. All ages
Propyderm 20% (Propylene glycol 200 mg/g)	Dry skin of different origin. All ages
Miniderm Duo (20 mg/g urea + 200 mg/g glycerol cream)	Dry skin. All ages
Oviderm cream (250 mg/g propylene glycol)	Dry skin. All ages

Source: Table 2.5.2, clinical overview.

II.2 About the product

Canoderm Duo is a lotion in form of oil-in-water (o/w) emulsion for topical use containing 50 mg/g urea and 200 mg/g propylene glycol belonging to the ATC group D02AE51 “Protectives and Emollients”.

Urea acts as a humectant with anti-pruritic and protective effects, and propylene glycol is a widely used humectant that increases the moisture in the skin. Propylene glycol also provides some antimicrobial properties to the product.

A national scientific advice was taken place on 2022-04-20.

The Applicant has received a full waiver for the pediatric population.

A proof-of-concept study in humans was assessed as not necessary since all ingredients have a long history of well-established use in humans.

Both urea and propylene glycol in the present medicinal product are well-known ingredients used for treatment of dry skin as monotherapy formulations.

II.3 General comments on the submitted dossier

The application for Canoderm Duo, 50 mg/g + 200 mg/g, Cutaneous emulsion, is a Combination Art. 10b application submitted according to Directive 2001/83/EC. The applicant applies for a marketing authorisation in Sweden through a National Procedure.

The active substances are not considered as new active substances.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The MPA has been assured that acceptable standards of GMP are in place for these product types at all

sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the European Community, the MPA has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GMP active substances
Regarding the statement on GMP for the active substance statements/declarations are provided from the manufacturer responsible for manufacture of the finished product and batch release situated in the EU.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

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.

Drug 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.2 Non-clinical aspects

Pharmacology
The primary pharmacology of propylene glycol is considered well-established after a long history of use in approved dermatological medical products. Briefly, propylene glycol diffuses into the stratum corneum and retains water in the skin resulting in a moisturizing effect. Urea has keratolytic and hydrating effects in the skin, possibly by breakage of hydrogen bonds in the stratum corneum, loosening epidermal keratin, and increasing water-binding sites.
Limited secondary- and safety pharmacology data with unclear clinical relevance have been presented. However, given the limited systemic exposure expected and the well-established use of the substances, no effects related to the secondary pharmacology or safety pharmacology of the substances are anticipated.

Pharmacokinetics
Based on referenced dermal penetration studies in animals and ex vivo studies in human biopsy skin specimen, the dermal penetration and systemic absorption and of propylene glycol is expected to be very limited. This is related to the very water-soluble properties of the substance. Nevertheless, given that e.g. emollients and emulsifiers are added to the Canoderm Duo formulation, the penetration of propylene glycol from dermal use of Canoderm Duo may theoretically increase compared to when it is given as a single agent.

Skin penetration studies with urea using intact and abraded human abdominal as well as dorsal skin from rats have shown that penetration across the skin was around 10% in intact skin, while abraded human skin dramatically increased the urea penetration. Given that urea is a normal constituent of skin and levels are also found systemically, these data support likely transport of urea across skin but that the levels reached are not expected to have any systemic significance. This is also in line with previous long-term experience from dermal use of urea-containing creams.

Collectively, the data referenced support that no to low levels of propylene glycol and urea may reach systemic circulation with dermal use of products which contains these substances, such as Canoderm Duo. Further, if the substances are applied to abraded skin, the transport across the skin may increase. However, it is not anticipated that higher levels of urea and propylene glycol will be reached with Canoderm Duo compared to the use of other similar and already approved products containing these APIs.

Toxicology
Literature data have been used to support the toxicology section. Single-dose toxicity studies with high doses identified CNS as a target organ of toxicity for both urea and propylene glycol. This information is of limited relevance for the dermal use of the product in accordance with treatment recommendations.
Several repeated-dose toxicity studies with propylene glycol and urea using various routes of administration have been referenced. No clear target organs of toxicity were identified, and the overall impression based on these studies is that the substances are well tolerated at doses likely exceeding the systemic levels which can be reached with the clinical use of Canoderm Duo.
There are no genotoxicity concerns associated with dermal administration of propylene glycol and urea, and chronic oral carcinogenicity studies in rats and mice do not support that urea and propylene glycol are carcinogenic substances.
Limited DART studies in mouse, rat and rabbit did not identify embryotoxic effects of urea or propylene glycol.

Local Tolerance
Given that propylene glycol and urea have been used for decades in dermal preparations at the concentrations used in Canoderm Duo, there are no additional local tolerance concerns for this product. All excipients, except butyrospermum parkii butter concentrate and nicotinamide, have been used in medical products before.

Regarding butyrospermum parkii butter concentrate, the Applicant provided a safety assessment. The collective impression is that the excipient is widely used, and there are no apparent toxicological concerns for the use of Butyrospermum Parkii Butter Concentrate at the specified level in Canoderm Duo.

To support the use of nicotinamide in the Canoderm Duo product, the Applicant has referenced non-clinical toxicity data and clinical safety data. Briefly, the systemic toxicity of nicotinamide is considered low, the substance is overall considered non-genotoxic and not irritating or sensitizing. Therefore, based on the data provided and the wide use of nicotinamide in cosmetic dermal

preparations, the use of the substance in Canoderm Duo is supported at the specified level from a toxicological point of view.

Environmental Risk Assessment (ERA)
The Applicant has submitted an ERA containing both urea and propylene glycol. Regarding urea, it is agreed that no further ERA data are necessary, as the substance can be considered a very common biomolecule and thus a natural part of the environment. Based on the common presence in the environment, this product is unlikely to alter the environmental concentration or distribution of urea. For this national approval, the ERA submitted for propylene glycol was considered acceptable, and the ERA concluded that propylene glycol is currently exempted from environmental risk assessment.

III.3 Clinical aspects

Pharmacokinetics
No pharmacokinetic studies have been performed on Canoderm Duo.

For urea, an endogenous substance already present in the skin, dermal absorption is not expected to increase, rather to be very limited. For the urea component of the drug product the distribution, metabolism and excretion is similar to endogenous urea.

For propylene glycol, a highly water-soluble substance, dermal absorption through the intact skin is expected to be very limited. There is however evidence that it is absorbed topically when applied on damaged skin. Propylene glycol is rapidly absorbed from the gastrointestinal tract, with maximum plasma concentration observed within 1 hour following oral intake in humans. Propylene glycol is absorbed via oral, intravenous, and rectal routes is primarily metabolized to lactic acid and pyruvic acid.

In summary, the systemic absorption of urea and propylene glycol is expected to be negligible after topical administration of Canoderm Duo on intact skin. Propylene glycol can be absorbed after topical application on damaged skin which is refelected with a warning in section 4.4 of the SmPC that Canoderm Duo should not be used on burned skin and information in section 5.2 of the SmPC that propylene glycol can be absorbed after topical application on damaged skin.

Pharmacodynamics
Canoderm Duo is a new light oil-in-water (o/w) emulsion for topical use, containing the two humectants urea (50 mg/g) and propylene glycol (200 mg/g). Lipids, together with other non-volatile ingredients, create a semi-occlusive layer on the skin surface, which fills in the fissures in dry skin and protects it physically from noxious factors, e.g., penetration of irritating substances. Moreover, this semi-occlusive layer, in combination with humectants present in the product (urea, propylene glycol), causes an increase of water content in the uppermost layer of the skin, stratum corneum, which otherwise is low in dry skin. Urea acts as a humectant with anti-pruritic and protective effects and propylene glycol is a widely used humectant that increases the moisture in the skin. Additionally, the long-term use of a moisturizer with 5 % urea has been shown to strengthen the skin barrier itself, which makes it more resistant to external factors. Furthermore, propylene glycol exerts some effect against bacteria and yeast.

The use of Canoderm Duo is hypothesized to strengthen the skin barrier in addition to improve skin hydration.

Clinical efficacy

Design and conduct of clinical studies
The product proposed for marketing, Canoderm Duo, contains 50 mg/g urea and 200 mg/g propylene glycol. The present application is supported by literature data, and by a Phase 2 trial to determine the superiority of the test treatment at strengthening the skin barrier as compared with no treatment and two reference treatments on non-lesional skin in patients with a history of AD. In the Phase 2 study, the IMP was compared to i) no treatment, ii) Propyless® and iii) Canoderm®. Propyless® contains 200 mg/g propylene glycol, and has skin hydrating properties whereas the 5% urea cream Canoderm®, is skin barrier strengthening.

All three products were applied on the lower inner forearms in a randomized scheme which is appropriate considering the aim of the study. The subjects included in the study were dosed twice daily for 28 days with the test products.

The primary objectives of the study were to determine whether applying Canoderm Duo for 4 weeks is superior in terms of skin barrier strengthening, when compared with i) no treatment or ii) Propyless®. A reduction in TEWL after induction of skin irritation was considered a skin barrier strengthening effect.

The secondary objectives were to determine whether Canoderm Duo is superior in terms of skin barrier strengthening when compared with Canoderm®, and to determine whether there is a difference between the test cream and no treatment and the two reference creams in resting skin barrier function, skin redness, irritant reactions, skin moisturization or pH, cream consumption and safety.

Efficacy data and additional analyses
In the Phase 2 study, most subjects (76%) were female. The mean age of the study population was 43 years. All patients were non-lesional at study inclusion. Most subjects (58%) had their last AD flare-up 1-2 years prior to the study start.

The study was performed in Germany. In total 55 patients were randomized and received study treatment. Twelve patients were excluded from the per protocol population due to important protocol deviations (n=11) or discontinued study treatment (n=1). The FAS comprised 55 participants and 43 participants qualified for the analysis in the PP population.

Summary of results obtained in the pivotal Phase 2b study – Co-primary endpoints
In the Phase 2 study, Canoderm Duo met the two co-primary endpoints which investigated skin barrier strengthening proporties after treatment with Canoderm Duo as compared with i) untreated control and ii) the skin barrier neutral lotion Propyless®. A significantly lower response from an irritating agent, measured as reduction of TEWL, was found after 4 weeks of treatment for Canoderm Duo® as compared with untreated control (p = 0,0010) and Propyless® (p =0,0010).

Summary of results obtained in the pivotal Phase 2b study – Secondary endpoints
The secondary efficacy endpoints demonstrate that, in the PP collective, the test product Canoderm Duo demonstrated a treatment effect on TEWL as compared with 1) no treatment and 2) Propyless®. The test product treated areas demonstrated results comparable to those of test areas treated with Canoderm®.

In terms of skin redness, the irritant caused significantly less redness in skin treated with Canoderm Duo compared to untreated skin (P=0.0293). No differences were seen when the test product treated areas was compared with Propyless® and Canoderm® treated areas.

Skin irritation was investigated through visual assessment and comparisons of irritant reactions (erythema, oedema, scaling, and fissures) before and after skin irritation test between Canoderm Duo and the reference products as well as no treatment. Canoderm Duo had equal performance as Propyless® and Canoderm® when change in mean score for erythema, scaling and fissures were investigated. Untreated skin had a significantly higher increase in erythema severity score as compared with Canoderm Duo treated areas. In terms of oedema, the mean severity scores were below the level of "slight oedema" for the differently treated as well as untreated test areas. The change in the mean score for Canoderm Duo treated areas was comparable to Canoderm® but significantly lower than that of the untreated and Propyless® treated test areas.

Skin capacitance measures showed that the skin hydrating effect of Canoderm Duo was not significantly different to Propyless®, Canoderm® or untreated areas.

Canoderm Duo had no effect on skin pH as compared with the reference treatments and no treatment. In terms of product consumption, there was no statistically significant difference between the test product and either reference product.

Literature data
The applicant has submitted literature data on treatment with dry skin with each of the active ingredients: urea or propylene glycol. No studies on the combination were available. These publications are assessed of limited relevance for the present application.

However, there is overall an extensive clinical experience with the use of urea and propylene glycol in adult patients in moisturizing creams. The active ingredients both have beneficial effect in individuals with dry skin disorders such as AD.

Conclusion on clinical efficacy
The product proposed for marketing contains a combination of the active ingredient's propylene glycol 20% and urea 5%. To date, there is no product with such combination on the Swedish market. The reference products included in the present study include the active components. Propylene glycol 20% is marketed in Propyless®, and urea 5% is marketed in Canoderm®. Both reference products used for dry skin of various genesis and have been available on the Swedish market since 2001 and 1998, respectively. This new fixed combination product enables cutaneous co-administration of propylene glycole and urea.

As stated in the *Guideline on clinical development of fixed combination medicinal products*, the combined use of the active substances in a FDC product is expected to improve benefit/risk by increasing efficacy and/or improving safety in comparison to the use of any of the single active substances. Increased efficacy has been demonstrated for the urea component as the combination is more effective than the monad propylene glycol in terms of TEWL. The contribution of propylene glycol to efficacy and/or safety or the usefulness of the product has been justified.

It is emphasized that the submitted Phase 2 trial is a pharmacodynamic study with a limited number of participants and an experimental design. Consequently, it is difficult to draw conclusions from the modest efficacy results obtained in the study. The hydrating effect of Canoderm Duo was not different from the reference treatments or the untreated control. With respect to reduction of TEWL, Canoderm Duo was shown to be superior to no treatment and to the reference cream Propyless,

Overall, the efficacy documentation presented for Canoderm Duo cream is considered adequate.

Clinical safety
The safety profile of the product proposed for marketing is benign and mainly dominated by local skin reactions. Data in the performed pharmacodynamic study shows that smarting/stinging reactions is comparable for Canoderm Duo compared to the reference monad products which is anticipated when combining two locally irritating substances. The combination of propylene glycol and urea is not anticipated to cause new or additional safety concerns compared to the monads. The proposed adverse event table in the SmPC section 4.8 is considered acceptable.

Overall, the safety documentation presented for Canoderm Duo cream is considered adequate.

Pharmacovigilance system
Proposed MAH: ACO Hud Nordic AB

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 Canoderm Duo.

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

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

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.1 signed 09 October 2024 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 RMS;
- 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.

Periodic Safety Update Report (PSUR)
Active substance is currently not listed in the published EURD list

The MAH shall submit the first periodic safety update report for this product with a period of 13 years (i. e. DLP of 13 years after authorisation) following authorisation. Further, MAHs shall continuously check the European medicines web-portal if the active substance has been included in the list of Union reference dates (EURD list). If yes, after publication in the EURD list the PSURs shall be submitted in accordance with the requirements set out in the EURD list.

Renewal date
The renewal date will be 5 years after approval date.

IV. BENEFIT RISK ASSESSMENT

Canoderm Duo is a moisturiser containing a combination of two active ingredients (urea and propylene glycol) that are previously well known as monads for treatment of dry skin of different origin.
There is an established clinical use of moisturising products with a variety of products approved which is of benefit for the user of the products since compliance to treatment is important. The benefits to patients with dry skin of different origin, for instance atopic dermatitis, is large where moisturizing products constitute the basic therapy. The risks are like other product in the same category, manageable and low.

The benefit risk of Canoderm Duo is positive.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments
N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**

N/A

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**

N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**

N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available on the Swedish MPA website.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available on the Swedish MPA website.

V.4.2 Assessment of User Testing

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 Oviderm 25 % cream regarding content and Canoderm 5 % cream regarding layout.
The bridging report submitted by the applicant has been found acceptable.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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