LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Miniderm Comp

(glycerol, urea)

SE/H/2080/01/DC
2020-0379

This module reflects the scientific discussion for the approval of Miniderm Comp. The procedure was finalised on 2021-03-09. 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

ACO Hud Nordic AB has applied for a marketing authorisation for Miniderm Comp, 20 %/2 %, cream. The active substances are glycerol and urea. Urea act as a humectant with anti-pruritic and protective effects and glycerol is a widely used humectant that increase the moisture in the skin.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10b of Directive 2001/83/EC (fixed combination).

The applicant has obtained a product specific PIP waiver from the PDCO/EMA for all subsets of the paediatric population for Miniderm Comp in the treatment of dry skin in adults, adolescents and children of all ages.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC 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

III.1 Pharmacology

The pharmacology of urea and glycerol has been described by the Applicant. The pharmacological rational for combining the two active substances is based on the well-established water binding properties of glycerol with the water binding and barrier strengthening abilities of urea.

Urea has keratolytic and hydrating effects which may be related to breakage of hydrogen bonds in the stratum corneum, loosening epidermal keratin, and increasing water-binding sites. Several effects of dermal glycerol have been described, including smoothing of the skin surface profile, reduction in electrical impedance and increases in the coefficient of friction. Further, glycerol has humectant properties, by which it increases skin hydration by binding water to the skin through extraction of moisture from the deeper layers of the skin. Overall, the primary pharmacodynamics of the two APIs is considered well-known for the intended use.

A brief presentation of other clinical applications of urea and glycerol has been provided by the Applicant. No secondary pharmacodynamics data haves been presented. However, given the dermal use and long-term clinical experience with the substances, this is considered acceptable.
No safety pharmacology data for glycerol or urea is presented by the Applicant. While such data is important in the (clinical) development of medical drugs, clinical experience supersedes any such information. Thus, given the extensive use of glycerol and urea for dermal preparations, these data are not considered useful or necessary for this Application.
Pharmacodynamic interactions have been described by the Applicant. According to drug interaction data referenced, 94 drugs are known to interact with urea, whereas 290 drug interactions with glycerol are known. However, given the low absorption of urea and glycerol expected at the proposed use of the product, and the long clinical experience with the drugs at the given concentrations, no important drug interactions are expected.

In summary, the pharmacodynamics presented for urea and glycerol is considered sufficient for the present indication and intended use of the product.

III.2 Pharmacokinetics

The pharmacokinetics of urea and glycerol has been described. Focus has been on skin penetration, since distribution, metabolism and excretion are considered of lesser importance for the present product. This is agreed.

For urea, three studies have been discussed with skin penetration studies in human abdominal skin, dorsal skin from female Osborne-Mendel rats and human keratinocytes and dermal fibroblasts. Briefly, in human abdominal skin, median in vitro absorption of urea in skin from 22 subjects was determined to be 11.1% of the applied dose. Further, in another study, the absorption of urea across normal and abraded human skin was 9.5%±2.3% and 67.9%±5.6%, respectively suggesting that abrasion of the skin increases the absorption. The same trend was seen in normal and abraded rat skin. No data was provided for glycerol, but only an estimation of absorption through intact skin for propylene glycol, which is claimed to be a similar substance.

Collectively, the data provided show that urea is rather well-absorbed over human and rat skin in vitro. However, given that only 2% will be used in the products applied for in this Application, the absolute levels absorbed will be small. While no data has been provided for glycerol, the plasma levels reached in the clinic at intended use are considered limited.

III.3 Toxicology

A toxicology programme based on published studies has been submitted by the Applicant. None of the studies are GLP compliant, which is considered acceptable. Considering that the Application is an Article 10(b) of Directive 2001/83/EC (Fixed combination), the focus of the non-clinical part should be on the combination studies. However, no such studies have been identified by the Applicant, and none have been submitted. Urea and glycerol have been combined in dermal products for decades, and the therapeutic value of the combination is well-established clinically. Further, the dermal toxicity profile of the individual components alone and in combination is considered known. Therefore, the lack of combination toxicity studies is acceptable.

As the individual products (urea and glycerol) are already approved in the concentrations applied for, the submitted studies on the individual substances are of limited regulatory relevance.

Single-dose toxicology studies for glycerol and urea have been provided but are considered of limited relevance for the present application. While no new data has been generated for this Application, it should be pointed out that LD50-values are no longer considered appropriate and should not be produced. That said, the data provided show that the acute toxicity of urea and glycerol is low. Repeat-dose toxicity studies with urea in rats showed that when rats and mice received daily diets with 4.5 % urea over a period of one year, no toxic effects were noted. While negative, not data on toxicokinetics or even proof of exposure is mentioned. Given that the study administered the urea via the feed, the lack of toxicokinetics makes a clear interpretation of the study difficult. Regarding glycerol, the Applicant makes reference to a publication from bibra (ref. 26). Based on the referenced data, target organs of toxicity of glycerol after oral administration include the GI system and the kidneys. However, while informative, the studies overall used doses and routes of administration with limited relevance for the present application.

Urea is not considered mutagenic. Further, it is agreed that the positive results obtained in some in vitro clastogenicity assays are associated with concentrations in excess of the recommended limit concentrations. They are therefore not considered to be of limited relevance. Glycerol is not considered a genotoxicant.

While the Applicant has referenced several carcinogenicity studies with positive findings in rats and mice, the findings were considered unrelated to treatment. Urea and glycerol are not considered to have a carcinogenic potential.
Several DART studies have been referenced by the Applicant. None of them was performed in accordance with available guidance documents on reproductive- and developmental toxicity studies. However, based on the studies presented, urea and glycerol have no adverse effects on reproduction and development. Further, given the minimal systemic exposure expected, no effects on reproduction or development are likely. This is also reflected in SmPC section 4.6. It is further noted that the Applicant has received a full waiver for the paediatric population and that no clinical trial in children is planned.

To conclude, while no combination toxicity studies have been submitted to support this fixed-dose Application, the study programme provided is still considered sufficient. There are no systemic safety concerns, and the local dermal effects are likely within what would be expected from topical application of urea and glycerol as individual substances.

III.4 Ecotoxicity/environmental risk assessment

The Applicant has provided an ERA in accordance with available guidance documents. Urea and glycerol are biomolecules present in most if not all species, and they are a natural part of the environment. Based on their common presence in the environment, these products are unlikely to alter the concentration or distribution of glycerol and urea in the environment.

IV. CLINICAL ASPECTS

IV.1 Pharmacodynamics

Topically applied urea has keratolytic and hydrating effects in the skin. The exact mechanism of action of urea in the skin is still unknown. Studies suggest that the keratolytic and hydrating effects of topical urea is owing to breakage of hydrogen bonds in the stratum corneum, loosening epidermal keratin, and increasing water-binding sites. By possibly breaking hydrogen bonds, and interfering with the quaternary structure of keratin, urea disperses and denatures keratin without disrupting the epidermal water barrier.

Glycerol on the other hand is a humectant, i.e. it increases skin hydration by binding water to the skin and affects the transepidermal water loss (TEWL). Miniderm Comp is an o/w emulsion, and glycerol prevent dehydration significantly, but less efficiently in an o/w emulsion compared with a w/o

emulsion. Glycerol in an o/w emulsion has a protective effect against irritants and induces a reconstitution of the protective skin barrier and initiates a regenerative skin protection in the skin.

The secondary pharmacodynamics effects of urea and glycerol has little clinical relevance when used topically since the systemic exposure of the active compounds is negligible.

In summary, urea act as a humectant with anti-pruritic and protective effects and glycerol is a widely used humectant that increase the moisture in the skin. They are both well-known active ingredients in topical formulations aimed for treatment of dry skin. The literature overview provided by the applicant is considered sufficiently detailed on pharmacodynamics.

IV.2 Clinical efficacy

Design and conduct of clinical studies

The applicant claims the indication treatment of dry skin in individuals of all ages including children. The application is supported by literature data, and by a Phase 2b trial to determine the superiority of the test treatment at strengthening the skin barrier compared to no treatment, and two reference treatments, in adults with predisposition to a skin barrier defect.

The Phase 2b study enrolled male and female patients 18 years of age or above having mild to moderate atopic dermatitis. The product proposed for marketing was compared to no treatment, Miniderm® 20% cream and Diprobase® cream (paraffin). The justification for omitting a treatment arm with urea 2% (20% glycerol would have to be removed from the formula and replaced by water, which would lead to heavy growth of bacteria in the cream) is accepted. The comparator arm with glycerol 20% (Miniderm®) is acknowledged since Miniderm® is an extensively used moisturizer in children, the main target population of this application. Miniderm® has shown to be neutral to the skin barrier i.e. not improving skin barrier function. Moreover, a paraffin cream (Diprobase®) was used as the other comparator arm. Diprobase® cream has shown skin hydrating properties but did not display an ability to actively improve sustained skin barrier function, i.e. it is a skin barrier neutral cream.

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 (± 3) days with the test products.

In total 50 patients were randomized and received study treatment.

The primary endpoints of the study were to determine whether applying the test cream for 4 weeks was superior in terms of skin barrier strengthening ability, when compared with no treatment and two reference creams in adults with a predisposition to a skin barrier defect. A reduction in Trans Epidermal Water Loss (TEWL) and in skin redness after induction of skin irritation was considered as a skin barrier strengthening effect.

The secondary efficacy endpoints in the study were 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 moisturization, tolerability, cream consumption and safety.

To measure skin strengthening ability by TEWL, and other techniques performed in the Phase 2b study is considered well established and accepted.

The statistical analysis performed is overall considered adequate.

Efficacy data and additional analyses

In the Phase 2b study, most subjects were female. The mean age was 38 years of age. Most subjects were Caucasians and had mild atopic dermatitis.

The study was performed in UK. Study completion was high in all treatment groups. Only one subject withdrew from the study, this subject was lost to follow up.

Summary of results obtained in the pivotal Phase 2b study – Co-primary endpoints
In the Phase 2b study, Miniderm Comp met the two co-primary endpoints which investigated skin barrier function after treatment with Miniderm Comp, compared to untreated control and two reference creams that do not affect skin barrier function. A significantly lower response from an irritating agent, measured as reduction of TEWL, was found after 4 weeks of treatment for Miniderm® cream compared with untreated control, Miniderm® and Diprobase®. The difference was larger compared with Diprobase® then with Miniderm® which is expected since the pharmaceutical profile of Miniderm Comp and the marketed Miniderm® is more similar compared with Diprobase®.

Measurement of skin redness, both visually and by Mexameter, showed that Miniderm Comp was significantly better than untreated skin and skin treated with Diprobase® cream to protect from skin irritation. There was no significant difference in the effect of Miniderm Comp compared to Miniderm® cream on skin redness.

Summary of results obtained in the pivotal Phase 2b study – Secondary endpoints
The study was not designed for a pass/fail approach to the secondary objectives. However, some tendencies were identified:

Skin capacitance measurements showed that Miniderm Comp had a hydrating effect compared to no treatment and was superior to Diprobase® cream. The skin hydrating effect of Miniderm Comp was not significantly different to Miniderm® cream.

Skin surface dryness was reduced after treatment with Miniderm Comp and Miniderm® cream, while treatment with Diprobase® cream left the skin as dry as the untreated control.

Participant tolerability was equally good for all three creams, as shown by both scoring of smarting/stinging sensation by participants, and objectively by measurement of skin erythema.

Literature data
The applicant has submitted literature data on treatment of children with dry skin with glycerol, or the combination glycerol and paraffin. 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 glycerol in adult patients, most often as monads, in moisturizing creams, but also in combination as reviewed by the Applicant. The active ingredients both have beneficial effect in individuals with dry skin disorders, and in patients with dry and irritated skin due to environmental and behavioral factors.

There is also extensive clinical experience with the monads, glycerol 20% cream (Miniderm®) and urea 2% in an extempore formulation prescribed on a named patient basis for treatment of dry skin in children and adolescents. From an efficacy perspective, there are no concerns for lack of efficacy in children. Moisturisers are the mainstay for treatment of AD and other skin diseases characterized of dry skin in children as well as in adults. Local tolerance, and its implications on compliance, are issues of importance for treatment success in children (see safety section below).

IV.3 Clinical safety

Presented data do not demonstrate any significant concern and the safety profile is mainly dominated by local skin reactions. As the presented phase 2 b study included a limited number of patients, the conclusion of the safety profile is supported by publications and the safety evaluation of approved moisturizers containing urea and glycerol.

There are no safety concerns in relation to combination treatment of glycerol and urea. Glycerol 20%

is approved (Miniderm®) and extensively used in all age groups. The concentration of urea is lower in Miniderm Comp in comparison to other urea containing moisturizers. The combination of glycerol and urea is not anticipated to cause new or additional safety concerns compared to the monads.

IV.4 Risk Management Plans

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 Miniderm Comp.

Safety specification

Table SVIII.1: Summary of safety concerns

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

Pharmacovigilance Plan

Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection will be conducted.

Additional pharmacovigilance activities

No additional pharmacovigilance activities will be conducted.

Summary of the pharmacovigilance plan (RMP Part III.5)

Not applicable.

Risk minimisation measures

Routine Risk Minimisation Measures

Not applicable, as no safety concerns have been considered important for inclusion in the RMP for Miniderm Comp.

Additional Risk Minimisation Measures

Not applicable, as no safety concerns have been considered important for inclusion in the RMP for Miniderm Comp.

Summary of Risk Minimisation Measures

Not applicable, as no safety concerns have been considered important for inclusion in the RMP for Miniderm Comp.

Summary of the RMP

The updated Risk Management Plan, version 0.2 signed 03 July 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 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.

IV.5 Discussion on the clinical aspects

The product proposed for marketing, contains a combination of the active ingredient's glycerol 20% and urea 2%. Glycerol 20% is marketed in Miniderm®, a product that is extensively used in children with atopic dermatitis and in individuals irrespective of age with sensitive skin. There is no product on the market with 2% urea. Since 5% urea might induce a stinging sensation, the combination of 2% urea and 20% glycerol as in the proposed product, may be beneficial in children and in other individuals with sensitive skin.

A significantly superior efficacy measured as skin strengthening ability was noted for Miniderm Comp compared with no treatment and paraffin (Diprobase®). The efficacy was slightly higher for Miniderm Comp compared to glycerol alone (Miniderm®), although not as statistically convincing. It should however be kept in mind that the study is a pharmacodynamic study with an experimental design and not a clinical efficacy study where clinical endpoints and benefits for the patients are evaluated.

There is extensive clinical experience with the monads, glycerol 20% cream (Miniderm®) and urea 2% in an extempore formulation often prescribed on a named patient basis to children.

There are no safety concerns in relation to combination treatment of glycerol and urea. Glycerol 20% is approved (Miniderm®) and extensively used in all age groups. The concentration of urea is lower in Miniderm Comp in comparison to other urea containing moisturizers. The combination of glycerol and urea is not anticipated to cause new or additional safety concerns compared to the monads.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Canoderm 5 % cream (urea), SE/H/556/01/P/10. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Miniderm Comp contains a combination of the active ingredient's glycerol 20% and urea 2% and is approved for treatment of dry skin in all age groups including infants and children. Glycerol 20% is marketed in Miniderm®, a product that is extensively used in children with atopic dermatitis and in individuals irrespective of age with sensitive skin. There is no product on the market with 2% urea. Since 5% urea might induce a stinging sensation, the combination of 2% urea and 20% glycerol as in Miniderns Duo, may be beneficial in children and in other individuals with sensitive skin.

Miniderm Comp have been formulated without preservatives which can be of advantage for patient groups who are sensitive to preservatives. The formulation is claimed to be self-preserved, but no in-use stability study has been performed to show preservation efficacy. The in-use shelf life has therefore been set to one month to reduce the risk of potential microbial contamination of the product.

A significantly superior efficacy measured as skin strengthening ability was noted for Miniderm Comp compared with no treatment and paraffin (Diprobase®) in a performed Phase 2b study. The efficacy was slightly higher for Miniderm Comp compared to glycerol alone (Miniderm®), although not as statistically convincing. It should however be kept in mind that the study is a pharmacodynamic study with an experimental design, and not a clinical efficacy study where clinical endpoints and benefits for the patients are evaluated.

There is extensive clinical experience with the monads, glycerol 20% cream (Miniderm®) and urea 2% in an extempore formulation often prescribed on a named patient basis to children in Sweden.

The safety profile noted in the performed phase 2b study is mainly dominated by local skin reactions. As the study included a limited number of patients, the conclusion of the safety profile is supported by publications and safety evaluation of approved moisturizers containing urea and glycerol.

There are no safety concerns in relation to combination treatment with glycerol and urea. Glycerol 20% is approved (Miniderm®) and extensively used in all age groups. The concentration of urea is lower in the Miniderm Comp in comparison to other urea containing moisturizers. The combination of glycerol and urea is not anticipated to cause new or additional safety concerns compared to the monads.

The benefit/risk ratio is considered positive and Miniderm Comp 20 %/2 %, cream is therefore recommended for approval.

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

Description	Due date
The validation for the filling and packaging steps of the manufacturing as described in 32P35 shall be finalized before the product is marketed.	Before the product is marketed

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

N/A

VII. APPROVAL

The decentralised procedure for Miniderm Comp 20 %/2 %, cream was positively finalised on 2021-03-09.

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