Inclusion of urea- and glycerol-based topical moisturizers on the EML and EMLc for the treatment of atopic dermatitis in adults and children

Applicants:

International Society of Atopic Dermatitis

Co-Applicant:

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Content

The following abbreviations are used in this application:

AAD: American Academy of Dermatology **AD**: atopic dermatitis **ASDV**: African Society of Dermatology & Venereology **ATC**: Anatomical Therapeutic Chemical **CI**: Confidence Interval **EASI**: Eczema Area and Severity Index **EML**: Model list of Essential Medicines **EMLc**: Model list of Essential Medicines Children **FTU**: Fingertip Unit **FDA**: Food and Drug Administration **GBD**: Global Burden of Disease **GRADE**: Grading of Recommendations, Assessment, Development and Evaluation **IGA**: Investigator's Global Assessment **INCI**: International Nomenclature of Cosmetic Ingredients **INN**: International Nonproprietary Names **ILDS**: International League of Dermatological Societies **ISAD**: International Society of Atopic Dermatitis	**MD**: mean difference **MPA**: Medical Product Agency **NMF**: Natural Moisturising Factor **NTD**: Neglected Tropical Diseases **OTC**: Over the counter, i.e. prescription-free **PCA**: Pyrrolidone Carboxylic Acid **Ph.Eur**: European Pharmacopoeia **QoL**: Quality of Life **RCT**: randomized controlled trial **RR:** Risk Ratio **SCCS**: Scientific Committee on Consumer Safety **SCORAD**: SCORing Atopic Dermatitis **SD**: Standard Difference **SLS**: Sodium Lauryl Sulphate **SMD**: Standardized Mean Difference **SRRC**: "Scaling Roughness Redness Cracks" **TCI:** topical calcineurin inhibitor **TEWL:** transepidermal water loss **TCS**: topical corticosteroids **USP**: US Pharmacopoeia **VAS**: visual analogue scale

Section 1: Summary statement of the proposal

This submission is based on the request of dermatologists practicing in the WHO-AFRO region who have difficulties accessing moisturizers for treating their patients. The submission is made in support of the inclusion of the humectants carbamide (urea) 5% and glycerol 15-20% in moisturizing creams on the core list of the EML and EMLc, for the treatment of atopic dermatitis (in adults and children). The term *moisturizer* is often used synonymously with emollient, but moisturizers usually also contain humectants in addition to fats and oil, aimed at further increasing the benefit on the skin.

Atopic dermatitis (AD) (also known as atopic eczema (AE)) affects more than 2% of the world population (with a peak prevalence in childhood). It is influenced by factors such as genetics, environmental conditions, and hygiene practices. AD is characterized by dry, itchy, and inflamed skin, which can lead to discomfort, sleep disturbances, and a reduced quality of life. In addition, psychological distress and social stigma are commonly associated - particularly in resource-constrained settings where access to healthcare and dermatological treatments is limited. Frequently in this setting, secondary skin infections develop on scratched eczematous skin when left untreated, leading to impetigo, cellulitis or septicemia which can have serious health implications.

International guidelines recommend moisturizing creams together with topical corticosteroids as the first line in the stepped treatment approach of AD. However, moisturizing creams are not identical but can contain different ingredients and comply with different regulatory categories, such as e.g. medicinal products, medical devices and cosmetics. The sets of legislations that apply for a certain moisturizing product are determined by its presentation, mechanism of action, composition and physiological effects.

Therefore, to facilitate the access of good quality products for treatment of AD in low-resource settings and select among the several hundred moisturizing creams on the market, the present application is based upon a multifaceted methodology where the clinical evidence and approval by national authorities are weighted high in the process. The availability, local compounding, cost, and cost-effectiveness in treatment of AD are also considered.

Our methodology identified 5% urea (INN carbamide) as the primary moisturizer in a defined cream base for treatment of AD. Urea is included on the WHO EML and EMLc list since 1995 (10%) and 2011 (5%) as a keratolytic agent. As a therapeutic alternative to urea, two moisturizing creams containing glycerol 15% and 20%, respectively, are proposed under a square box listing. We also recognize the critical importance of the excipients in moisturizers for the final safety, efficacy and cosmetic attributes.

Section 2: Consultation with WHO technical departments

WHO skin NTDs team (Dr Kingsley Asiedu), co-applicant, - in charge of non-communicable chronic skin diseases within the 2022 strategic framework program for skin health (JA Ruiz Postigo)-, Department of Control of Neglected Tropical Diseases, WHO's Division of Universal Health Coverage/Communicable and Noncommunicable Diseases, WHO HQ Geneva.

WHO AFRO (Dr Abate Beshah, Dr Matshidiso Moeti)

Section 3: Other organization(s) consulted and/or supporting the submission

The composition of the writing group for the submission was as follows: Alain Taieb (Dermatologist, ISAD France, Chair), Marie Loden (Pharmacist and Dermatologist, Eviderm Institute AB Sweden, Co-chair), Peter Schmid-Grendelmeier (Dermatologist, ISAD Switzerland), Andreas Wollenberg (Dermatologist, ISAD Germany), Erere Otrofanowei (Dermatologist, ASDV, ISAD Nigeria), Ousmane Faye (Dermatologist, ISAD Mali), Gianni Baratto (Pharmacist, UNIFARCO, Italy), Andrea Baratto (Pharmacist, UNIFARCO, Italy), Roberta Milani (Pharmacist, UNIFARCO, Italy), Sophie Weber (Engineer, NAOS, France)

Supporting Organizations:

- ASDV (African Society of Dermatology and Venereology)
- ILDS (International League of Dermatological Societies). Both ISAD and ASDV are affiliated to the ILDS
- Global Skin (International alliance of Dermatology patients' organizations)

Letters of support in **ANNEX 4**.

Consultations were organized with several leading manufacturing companies during the preparation of this application namely L'Oreal (Bertand Chuberre), Beiersdorf (Adel Sammain), Pierre Fabre (Jean Jacques Voisard)

Section 4: Key information summary for the proposed medicine(s)

Table 1. Key information summary for the proposed medicines.

INN	Carbamide (urea)		
ATC code	D02AE01		
Indication	Atopic dermatitis		
ICD-11 code	EA80 Atopic eczema		
Dosage form	**Strength**	**EML**	**EMLc**
Cream	5%	Yes	Yes

Excipients: Triglycerides medium chain, polysorbate 60, cetostearyl alcohol, hydrogenated canola oil, propylene glycol, carbomer, dimethicone, hard paraffin, glycerol polymethacrylate, ethyl parahydroxybenzoate (E 214), methyl parahydroxybenzoate (E 218), sodium lactate solution, lactic acid, glyceryl stearate, polyoxyethylene stearate, purified water.			
INN	Glycerol		
ATC code	D02AX		
Indication	Atopic dermatitis		
ICD-11 code	EA80 Atopic eczema		
Dosage form	**Strength**	**EML**	**EMLc**
Cream	20%	Yes	Yes
Excipients: Hydrogenated canola oil, cholesterol, glycerol monostearate, macrogol stearate, cetostearyl alcohol, dimeticone, light liquid paraffin, hard paraffin, white soft paraffin, ethyl parahydroxybenzoate (E 214), methyl parahydroxybenzoate (E 218), purified water.			
INN	Glycerol + liquid paraffin + white soft paraffin		
ATC code	D02AC		
Indication	Atopic dermatitis		
ICD-11 code	EA80 Atopic eczema		
Dosage form	**Strength**	**EML**	**EMLc**
Cream	15% glycerol + 2% liquid paraffin+ 8% white soft paraffin/petrolatum	Yes	Yes
Excipients: glycerol monostearate, stearic acid, polydimethylcyclosiloxane, silicone oil, macrogol 600, trolamine, propyl parahydroxybenzoate (E216) and purified water.			

The International Non-Proprietary Names (INN) are primarily used in the present application, but the International Nomenclature Cosmetic Ingredient (INCI) names may also be used when appropriate, e.g. when the scientific publications are discussed. Therefore, carbamide (INN) corresponds to urea (INCI), and glycerol (INN) to glycerin (INCI).

The indication EA80 Atopic Eczema (also known as Atopic Dermatitis; AD) is defined by the International Classification of Diseases, 11th revision (ICD-11) *(1)*:

"*A chronic inflammatory genetically determined eczematous dermatosis associated with an atopic diathesis (elevated circulating IgE levels, Type I allergy, asthma and allergic rhinitis.). Filaggrin mutations resulting in impaired epidermal barrier function are important in its pathogenesis. Atopic eczema is manifested by intense pruritus, exudation, crusting, excoriation and lichenification. The face and non-flexural areas are often involved in infants; involvement of the limb flexures may be seen at any age. Although commonly limited in extent and duration, atopic eczema may be generalised and life long*."

Section 5: Listing as an individual medicine or representative of a pharmacological class / therapeutic group

Introduction

This submission proposes the inclusion of one carbamide-based and two glycerol-based moisturizer creams registered for the indication dry skin in patients diagnosed with AD in the core list of the EML and EMLc. The proposal is based on two sets of criteria: conditional and operational (Figure 1).

The conditional criteria include literature evidence, pathophysiology guidance for the choice of ingredients, technical aspects for manufacturing products, and production costs. The operational criteria include giving preference to substances and products already registered by regulatory agencies within the ATC-system in the emollient and protective category D02A, and to reflect the ranking within the systematic reviews for the indication AD. The final decision is based on a consensus of the writing group and endorsement by supporting organizations.

Our multifaceted methodological approach agrees with the conclusion of a systematic review emphasizing that "*... the clinical effect appears to be much more well-documented for urea and glycerin than, for example, propylene glycol, lactate, ceramide, and aluminum chlorohydrate" (2)*.

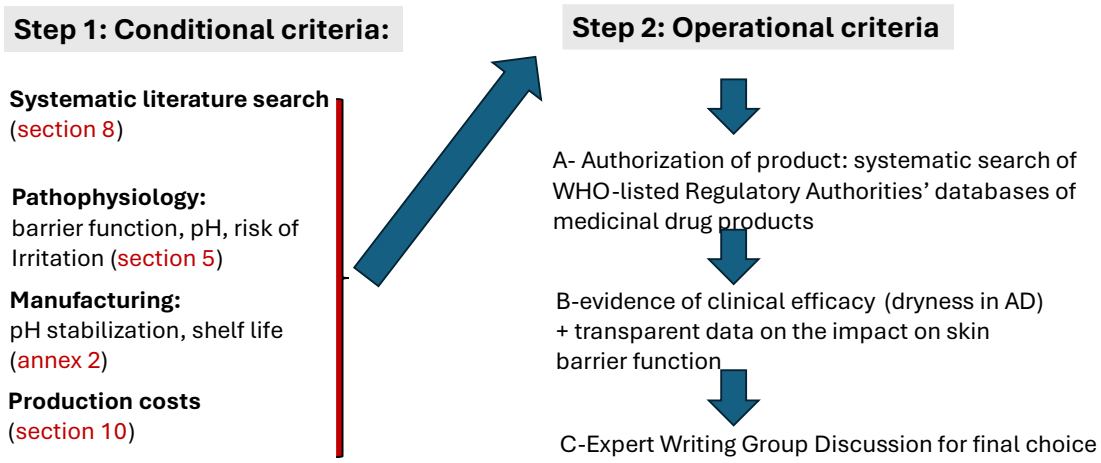


Figure 1. Moisturizers for AD: Criteria of choice for inclusion in EML and EMLc.

Methodology and results

Conditional criteria

1. Evidence from the literature:

The identified systematic reviews judged the clinical studies of moisturizers containing carbamide and glycerol positively and concluded that these creams were more well-

documented and more effective than their controls (vehicle, placebo or no moisturizer) according to both participants and physicians than for other tested substances *(2-5)*, see further discussion in the **systematic reviews** and additional data in **Section 8**.

2. Pathophysiology vs manufacturing considerations: optimizing skin pH, barrier function and limiting irritation:

The composition of the creams is important, since differences in composition influence not only the immediate effect on dryness relief, but also the effects on skin barrier function *(6-12)* with consequences for the prevention of eczema *(13)*. Notably, not only the active ingredient but also the selection of excipients is of utmost importance since some excipients may weaken skin barrier function and increase risks for eczema, see **Figure 2 and Annex 2**.

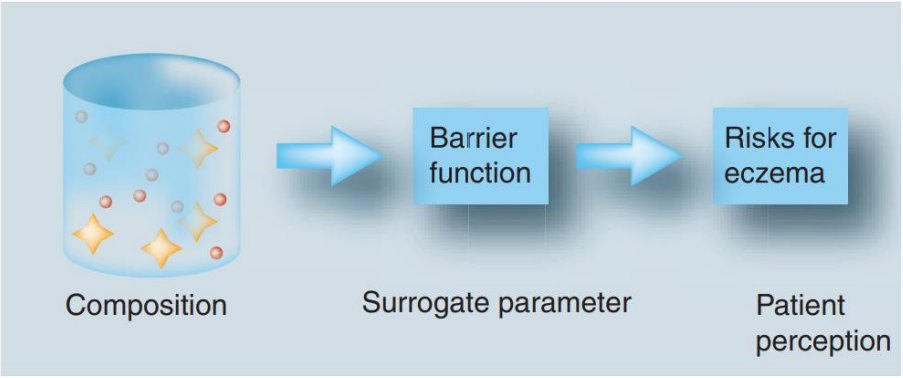


Figure 2. Proposed view on the risks for eczema related to the surrogate parameter barrier function. The composition of the moisturizer may induce changes in skin barrier function, measured as transepidermal water loss (TEWL), which is suggested to predict the likelihood of developing eczema, from *(11)* with permission.

Urea (carbamide) belongs to the Natural Moisturizing Factor (NMF) in the skin*(14)*. In AD skin the content of urea is reduced *(15)*, which is suggested to be due to stagnation in perspiration in AD skin *(16)*. Topically applied urea is easily absorbed into the skin after application *(16-18)*. Treatment of normal skin with moisturizers containing 5-10% urea has been found to reduce TEWL and to diminish the irritative response to the surfactant sodium lauryl sulphate (SLS) *(7, 19, 20)*. Similar results have also been found after repeated use of alcohol-based disinfectants, despite high content of ethanol *(21)*. Urea could protect against osmotic stress by replacing water and retain the liquid crystalline phase at lower humidity *(22)*.

The term “acid mantle” as a skin defence against bacteria was coined almost 100 years ago *(23)*. Higher pH values are observed in both lesional, perilesional and uninvolved AD skin, than skin in healthy controls *(24)*. The normally acidic skin surface and its gradual changes within the skin orchestrate epidermal differentiation and corneocyte shedding and therefore elevation of skin pH suggests impairment in the formation of a proper epidermal barrier *(25, 26)*. Colonization by *Staphylococcus aureus* is favoured by alkalinization *(27)* and is also linked to the weakened AD skin barrier function *(24, 28)*.

Most urea-containing creams, lotions, and ointments are formulated to be slightly acidic to ensure skin compatibility and stability of the product. Lactic acid is often used to control pH in

urea formulations. Pure glycerin is neutral, and its aqueous solutions usually exhibit a pH around 7. Commercial products with glycerin can easily be buffered to any pH value.

Transient skin reactions have been reported with topical urea, and some people might experience slight redness, itching, or a burning sensation at the application site. Higher concentrations (>10%) of urea may cause the skin to become excessively dry or start peeling. Therefore, 5% is the recommended concentration in this application, which corresponds to the lower concentration already listed in the EML/EMLc. A larger range of concentrations between 5 and 10% would be acceptable according to the final formulation, but 10% should be avoided in sensitive areas such as the face. However, optimizing urea concentration specifically for the indication AD may need in the future more clinical studies addressing efficacy vs limitation of local side effects and optimal compounding for pH.

Glycerol not only attracts water and increase skin hydration *(29)*, but is also suggested to modulate the phase behaviour of stratum corneum lipids and to enable the lipids to maintain the liquid crystal state and thus prevent crystallization of their lamellar structures *in vitro* at low relative humidity *(30)*. The biochemical consequences of these properties are increased activity of hydrolytic enzymes crucial to the desquamatory process *in vivo (31, 32)*.

Dryness in sebaceous gland deficient mice is linked to reduced levels of glycerol because of absence of triglycerides *(33)*. This type of dryness is suggested applicable to clinical situations where sebaceous glands are absent or involuted, such as in prepubertal children showing eczematous patches, which disappear with the onset of sebaceous gland activity. Moreover, xerosis in the distal extremities of aged skin and in patients receiving systemic isotretinoin for treatment of acne may be linked to glycerol depletion because of the lower sebaceous gland activity *(33)*.

Aqueous solutions of glycerol have been shown to reduce TEWL *(34)* for some hours after application and to stimulate barrier repair during the first days after SLS-damage in human skin *(35)*. Furthermore, glycerol is reported to decrease skin sensitivity to alkali, SLS and dimethyl sulfoxide, but to increase bioavailability of hexyl nicotinate *(36)*. However, in a 10-days RCT on forearm skin, no influence of 20% glycerol on human skin permeability barrier was observed, in terms of TEWL and skin sensitivity to SLS-induced irritation *(37)*.

3. Manufacturing: chemistry, stabilization, and shelf life

Carbamide (urea) is colourless, odourless (or nearly odourless), slightly hygroscopic prismatic crystalline substance with a cooling saline taste. It is produced industrially by a reaction of ammonia with carbon dioxide.

Carbamide is cheap and can easily be incorporated into dermatological preparations as it resembles the water molecule and is highly water soluble. It is almost insoluble in non-polar media. However, urea may give shorter shelf-life of medicinal formulations due to decomposition of urea into ammonium ions (NH4+) and cyanate (CNO−), which further undergo conversion to carbon dioxide (CO_2) and ammonia (NH_3) which increases pH. Due to increase in pH the shelf-life of medicinal preparations is usually restricted to 2 years at +25 ˚ C, despite less than 5-10% of urea is decomposed during this time *(38)*. Stability analyses of solutions and pharmaceutical preparations with 2.5%–20% urea showed highest stability in lactate buffer pH 6.0 *(38)*.

Glycerol (glycerin) is technically a solution of the trihydric alcohol glycerol. Glycerol is chemically stable and does not react with most substances. In closed containers and away from direct sunlight and extreme temperatures, it can remain stable for several years. It is hygroscopic, meaning it can absorb moisture from the air, but this does not affect its chemical structure. Glycerol is easily incorporated in moisturizing creams. In the treatment of dry skin conditions, levels of glycerol ranging between a few percent to 25% are used *(39)*.

Glycerol-based creams for the treatment of AD are proposed as a qualified square box option, even if the criterion "improvement of barrier function" is not equally well demonstrated as for urea-based formulations. When the two options are available on a given market, glycerol-based creams can be considered especially in case of patient preference. The usual concentration in compounding 15%-20% along with suitable excipients favouring the clinical benefit in AD.

4. Manufacturing costs

Differences concerning manufacturing costs are estimated to be minimal for the two selected categories of moisturizers, urea-based and glycerol-based (see **Section 10**)

Operational criteria

The main operative criteria were as follows:

A. **Their authorization by a National Competent Medicinal Authority** as a medicinal product to be used for treatment of dryness in adults and children with AD. The WHO-listed Regulatory Authorities' databases of medicinal drug products were used to identify emollients and protectives for treatment of dry skin of different origins, particularly AD. This increases the quality of the selected products, as their stability, safety and effectiveness are approved by external authorities. Products regulated in other categories (e.g. cosmetics) are generally not indicated and allowed to be presented in the treatment of diseases. But currently the OTC market is dominated by dermatological formulations for cosmetic uses which are used, sometimes with dermatological supervision as a marketing argument, for the treatment of diseases such as AD. However, their formulation does not match the more rigorous recommendations made in this application.
B. **Evidence of their clinical efficacy** regarding treatment of dryness in AD in all age groups along with transparent data on the impact on **skin barrier function**, which preferably should be positive (i.e. strengthened skin barrier function, e.g. lowering of TEWL, Fig 2) with reduced risks for eczema, see **Section 8: Review of evidence for benefits and harms**.
C. **Writing Group** discussion and final decision for recommendation: several versions of the draft were circulated and reviewed, and the advice of the WHO EML Secretariat was obtained at several stages of the preparation. A total of 4 virtual meetings of the WG was organized to discuss the draft of the application and reach consensus on sensible issues, and a final face to face meeting is scheduled on Oct 23, 2024, before the International Symposium on AD in Doha, Qatar.

Moisturizing creams authorized by national authorities and recommended in the present application are listed in Table 2A, where those listed but recommended against are listed in Table 2B.
The 5% urea-containing cream recommended in the present application is indicated for the "moisturising of dry skin of different origin and for prevention of relapse of atopic eczema" *(40)*,

shown in clinical studies on AD and hand-eczema *(41-43)*, see further **Evidence for comparative effectiveness of urea.**

The two recommended glycerol-moisturizers contain 15% and 20% glycerol, respectively. The water-binding activity of glycerol is acknowledged by the authorities to contribute to normalization of dry skin. Adjunctive treatment of dry skin conditions of certain dermatoses such as e.g. AD *(44)*.

In addition, their content of hydrophobic fat, such as e.g. petrolatum also contributes to their improved barrier function, see **Evidence for comparative effectiveness of glycerol.**

Summary of the recommendations and their rationale for EML and EMLc listing

The clinical evidence for efficacy and approvals by national authorities are weighted high in our process to identify good quality products for treatment of AD in low-resource settings.

The Regulatory Authorities' WHO-listed databases of medicinal drug products were used to identify emollients and protectives (D02A) for the treatment of AD. The authorized products along with their active ingredients and our recommendation for inclusion or against inclusion are given in Table 2A and B, respectively, based on the criteria regarding clinical evidence evaluated in **Section 8.**

TABLE 2A. Moisturizing creams recommended for inclusion on the EML and EMLc for treatment of atopic dermatitis in this submission. The products are also authorized by national authorities (code D02A emollients and protectives).

Active ingredients	Clinical evidence in AD, references	Effect on barrier function	Excipients
Carbamide 5%	Yes *(42, 43, 45-47)*	Improvement *(46, 47)*	Triglycerides medium-chain, polysorbate 60, cetostearyl alcohol, hydrogenated canola oil, propylene glycol, carbomer, dimethicone, hard paraffin, glycerol polymetacrylate, ethyl parahydroxybenzoate (E 214), methyl parahydroxybenzoate (E 218), sodium lactate solution, lactic acid, glyceryl stearate, polyoxyethylene stearate, purified water.
Glycerol 20%	Yes (30)	No influence (31)	Hydrogenated canola oil, cholesterol, glycerol monostearate, macrogol stearate, cetostearyl alcohol, dimeticone, light liquid paraffin, hard paraffin, white soft paraffin, ethyl parahydroxybenzoate (E 214), methyl parahydroxybenzoate (E 218), purified water.
Glycerol 15% Vaseline 8% Paraffine 2%	Yes *(48, 49)*	Limited data	Glycerol monostearate, stearic acid, polydimethylcyclosiloxane, silicone oil, macrogol 600, trolamine, propyl parahydroxybenzoate (E216) and purified water.

Table 2B. Moisturizing creams recommended against inclusion on the EML and EMLc, despite authorization by national authorities (code D02A).

Active ingredients	Clinical evidence in AD, references	Effect on barrier function	Recommended
Carbamide 10% Lactic acid 5%	Yes, but too acidic pH which limits clinical tolerance *(50-53)*	Improved in AD and in healthy skin *(54)* (ichthyosis) *(19)*	No
Carbamide 4% Sodium Chloride 4%	Yes *(45)*	No *(46)*	No
Carbamide 5% Macrogollaurylether 6 (polidocanol) 3%	Limited data	No data	No
Carbamide 2% Glycerol 20%	Limited data *(9)*	Conflicting, increase in TEWL *(9)*	No
Glycerol 10% Light Liquid Paraffin 10% White soft paraffin 5%	No data	No data	No
Propylene glycol 20%	No data	No data	No
Propylene glycol 25%	No data	No data	No
Propylene glycol 20% Lactic acid 4.5%	Ichthyosis *(55)*	Weakening *(55)*	No

Section 6: Information supporting the public health relevance.

According to the Global Burden of Disease (GBD) consortium, at least 171 million individuals were affected with AD in 2019, corresponding to 2.23% of the world population, with age-standardized prevalence and incidence rates that were relatively stable from 1990 to 2019 *(56)*.

The International Society of AD (ISAD) organized a roundtable on global aspects of AD at the World Congress of Dermatology 2023 in Singapore. Based on the panel experience, most AD cases are mild-to-moderate. Without parallel data on disease prevalence and severity, the GBD data are difficult to interpret in many regions. This gap is particularly important in countries with limited medical infrastructure, but indirect evidence suggests a significant burden of AD in low-and-medium resource settings, especially urban areas. The Singapore roundtable was an opportunity to compare experiences in low-income (Madagascar and Mali), upper-middle-income (Brazil, China) and high-income (Australia, Germany, Qatar, USA, Singapore, Japan) countries. The panel concluded that current AD guidelines are not adapted for low resource settings and a more pragmatic approach, as developed by WHO for skin NTDs, would be advisable for minimal access to moisturizers and topical corticosteroids. Collaboration with WHO, patient advocacy groups and industry may promote global change, improve capacity training, and fight current inequalities *(57)*.

In patients with AD the quality of life (QoL) is reduced by eczema *(58-61)*, where the stigma associated with its visibility *(62)* and the itch *(63)* affects children as well as adults. Sleeplessness may lead to poor work functioning and decreased skills *(64)*. Furthermore, eczema is a time-consuming and costly disease *(59)*, similar to the costs of other chronic diseases *(65)*. Suffering from AD results in a high individual, familial and social burden *(57)*.

As compared with other chronic skin and non-skin diseases, scores assessing the deterioration in QoL on the Dermatology Life Quality Index (DLQI, a validated QoL instrument) are among the highest in patients with AD *(66)*, and that the willingness to pay for complete healing is comparable to that for relief of other serious medical conditions, such as e.g. angina pectoris, chronic anxiety, rheumatoid arthritis or multiple sclerosis *(66)*.

Public health relevance and target populations *(67)*: Physical discomfort, psychological distress, and social stigma, are particularly marked in resource-constrained settings where access to healthcare and dermatological treatments is limited. When AD is left untreated, secondary skin infections can develop, including impetigo and cellulitis, and even septicemia, which can have serious health implications. Viral superinfection by herpes simplex may be life-threatening and is probably underdiagnosed *(57)*.For children, a major target population, vulnerability consequences include school absenteeism and decreased learning outcomes when itchy skin disrupts daily activities and sleep *(68)*.

Many low-resource settings, including parts of Sub-Saharan Africa, face challenges in providing access to specialized dermatological care and medications like moisturizers and TCS. This application concentrates on moisturizers which play a crucial role in preventing flare-ups, providing symptomatic relief, and improving skin barrier function. They need to be part of primary care interventions in those settings where comprehensive dermatological care is limited. However, public health interventions should simultaneously include strategies to promote the appropriate use of moisturizers and skincare education to improve the management of AD in these regions *(57, 69)*. This issue is highlighted in a recently published OpenWHO course on AD designed for the training of national and district-level health workers in Sub-Saharan Africa and similar settings *(69)*.

Section 7: Treatment details

General background concerning moisturizers

The term “moisturizer” has been used in the present application, even though the term “emollient” is sometimes used synonymously in different texts. The word emollient is derived from the Latin word molle or mollis, which means soft, pliable, and supple, that is, a material designed to soften the skin and “smooths” the surface to the touch and make it look smoother to the eye. Generally, emollients refer to oils/fats/lipids from vegetable and/or fossil sources, whereas moisturizers are usually emulsions which in addition to emollients also contain humectants (e.g. urea, glycerol) which “*retain and/or preserve moisture in a product during use*” (as described in the EU database on ingredients in cosmetics). Moisturizing is described in the EU database as “*Increasing the water content of the skin and keeping it soft and smooth*”. The most common type of moisturizer is a two-phase system (emulsion) containing emollients/ lipids/oil dispersed in the form of microscopic droplets in the water. The emulsifiers keep the

droplets separated during the shelf-life of the formulation. Lipids can be defined as substances biochemically or functionally related to fatty acids. Emulsifiers can also be classified as lipids.

Moisturizing creams belong to the most widely used preparations in dermatology and are the mainstay of management of AD in combination with TCS, as they relieve symptoms of dryness and prolong periods of healthy skin. Moisturizing creams differ in chemistry and function, and they comply with different regulatory categories, such as e.g. medicinal products, medical devices and cosmetics. Local products based on vegetal oils/waxes such as shea butter or coconut oil are not discussed in depth in the proposal because they are generally not of sufficient quality to provide a true alternative, see **Section 9**.

One of the major reasons of this submission is that moisturizing creams are mostly available as imported over the counter (OTC) products with high taxation as cosmetics in low resource settings and are as such not affordable for the patients in need of a baseline topical treatment (**see Section 10**). An extensive survey of this issue (availability and cost of moisturizers for AD) is ongoing through the ISAD-ASDV task force and should be available by the end of 2024.

The practical and economical process of treating the skin add to the burden of having the disease. It is known that stress can elicit exacerbations of the disease and perpetuate the itch-scratch cycle. Anxiety or depression are acknowledged comorbidities in AD. Furthermore, patients may be confused by the plethora of nonprescription products available, which not always deliver on their marketing promises.

Satisfaction with the cosmetic properties is also known to vary between different products. For example, in a recent 4 months study on 550 children (between 6 months and 12 years of age) it was found that what one family liked about a moisturiser was not necessarily the same for another and the preferences were individual to each user *(70)*. The emollient types were found to be equally effective, but the parents/children favoured different ones. Notably, in the cases when there was a tension between how well a moisturiser worked (effectiveness) and how easy it was to use (acceptability) the effectiveness tended to decide whether parents kept using it *(70)*. A lower adherence to the use of an ointment was also found in a study of an ointment vs cream of the same topical corticosteroid molecule, because of lower cosmetic acceptability *(71)*.

Treatment recommendation by a health care provider based on objective and reliable data is an important factor in moisturizer selection. Proper skin care instructions should be given when a moisturizer is prescribed, and patients should be informed about potential local mild, transient reactions, e.g. stinging, in sensitive skin areas which may occur especially in inflamed skin and in the beginning of the treatment.

In low-resource settings, the prescription of moisturizers for AD should take into consideration the immediate practicality, affordability, and accessibility of these products, as well as sustainability in the medium-long term. The dosage regimen and treatment duration are summarized below.

Application technique

The use of the fingertip unit (FTU) is recommended to monitor amounts used *(72-74)*. The FTU is defined as the amount of ointment expressed from a tube with a 5 mm diameter nozzle applied from the distal skin-crease to the tip of the index finger *(74)*.

Airless pump jars with dosing pumps are also used to facilitate precise dosing of creams. They also protect the cream from contamination, from e.g. micro-organisms. However, the cost of this type of packaging, and its environmental sustainability may limit usage.

One FTU is an adequate amount (ca. 0.5 g) for application to two adult palm areas, which is approximately 2% of an adult body surface area.

- For an adult male: 1 fingertip unit provides 0.5 g.
- For an adult female: 1 fingertip unit provides 0.4 g.
- For a child aged 4 years – approximately 1/3 of adult amount.

Dosage regimen

The moisturizers should be applied on affected skin and areas prone to eczema once daily or more frequently depending on skin dryness condition, especially after exposure to water.

Patients should use enough emollient to cover the affected areas generously. Insufficient application may not provide adequate benefit.

Adequate dosing is facilitated by recommended number of fingertip units *(72)* or number of pump strokes. See further information in **Section 8.**

The recommended quantities of emollients/moisturizers for treatment of AD vary based on factors such as the extent of the affected area, individual skin characteristics, and product consistency (e.g., cream, ointment). Uniform dosage for all age groups needs to be adapted to surface area. Experimental studies show that the distribution of a thick ointment differs to formulations with lower viscosity and more volatile ingredients (e.g. creams) *(75)*. Furthermore, the type of packaging also influence the dosing, and jars have been noted to promote use of larger quantities than the same cream in a tube (1.7 vs 0.7 mg/cm^2, respectively)*(76)*. However, it may be expected that moisturizer treatment seldom requires the same application rate on different sites, due to the various severities of the dryness in the treated areas.

The UK National Institute for Health and Care Excellence – NICE - recommends approximately 35-70 g per day to children, i.e. 250 g to 500 g leave-on emollients weekly *(77)*, which is similar to a European guidance documents for treatment of AD *(73, 78)* which recommends:

For adults: Applying approximately 250-500 grams of emollient/moisturizer per week, which translates to approximately 35-70 grams per day, is a common range. This quantity can be adjusted based on the severity of symptoms and personal preferences.

For children: The amount for children is generally less, starting with approximately 125-250 grams per week, or about 18-35 grams per day. Adjustments may be necessary depending on the child's age and the extent of their condition.

However, the rationale for these recommendations is not known and evidence is lacking with respect to the correlation between the treatment effects and the frequency of application and/or dosage per area. However, studies report improvements of symptoms of AD with increased use of moisturizers but these effects may well have been enhanced by the educational support program, general practitioner contacts and/or the use of corticosteroids used in the studies *(79, 80)*. One of the systematic reviews (Cochrane) also concludes that "*we are still unable to confirm how often moisturizers need to be applied*" *(3)*.

In a recent real-world study, the use of emollients, was found to be fourfold lower than the amount recommended in the cited guidelines *(81)*. The actual consumption in the real-world study, was 4.6 g-16.8 g per day, median 9.6 g, for adults, and between 12 g and 30 g per day (median 17.5) for juvenile patients *(81)*. The observed use varied between patients, but the median overall daily use was approximately 10 g (< 5 g in the lowest quarter) which was suggested to be due to no use of emollients for large time periods throughout the 1-year period *(81)*. These figures are in line with the EU Scientific Committee on Consumer Safety (SCCS), who states that the daily exposure level to body lotion is estimated to 7.82 g, where the lotion is estimated to be applied 2.28 times/day *(82)*. In addition, the amounts of cosmetic products applied to the skin usually do not exceed 1 mg/cm^2 under in-use conditions *(82)*.

Similar median consumption was reported in a one-month clinical trial of 197 AD patients, where the group treated with a glycerol-cream used approximately 10 g daily, the carbamide group used 11 g daily and the placebo group used 12 g daily, dispensed from a jar *(39)*. In another study on AD, the average daily-cream consumption was about 12 g during one month, where the patients were instructed to treat dry areas at least once daily, and their hands twice daily *(46)*.

Seasonal changes in the consumption of moisturizers with carbamide and glycerol products are also seen in statistics in Sweden, where less dispensations are seen in summer compared to winter (published by The National Board of Health and Welfare) *(83)*. In the year 2023, the number of patients in Sweden receiving reimbursed moisturizers (prescriptions) with carbamide was 33/1000 inhabitants, where the number of dispensations was 79/1000 inhabitants. The corresponding figures for glycerol are 26/1000 and 58/1000, respectively. No figures on the simultaneous use of OTC dispensation are reported.

Therefore, until further data are obtained regarding the dose-response in the treatment of AD with moisturizers, **a reasonable daily use can be expected to be about 10-20 g in adults** and less in children.

Duration of treatment:

Moisturizers play an important role primarily in maintenance therapy but also in conjunction with other anti-inflammatory treatment, such as e.g. TCS.

In low-resource settings, where access to specialized treatments may be limited, moisturizers can be used continuously as part of maintenance therapy. Patients should be advised to continue using emollients even when their skin appears to be in good condition to prevent flare-ups. The duration of treatment may vary from person to person. If the condition worsens or if complications like infections arise, more intensive therapies may be necessary. Patients should be educated about recognizing signs of disease exacerbation and when to seek medical attention.

Section 8: Review of evidence for benefits and harms

General summary of benefits

Evidence supporting the use of moisturizers as part of the treatment approach for AD is summarized below, and are developed in the following systematic reviews:

Improved skin hydration: Moisturizers are effective in improving skin hydration and reducing dryness in individuals with AD. They help to restore and maintain the skin barrier function, which is impaired in this condition.

Reduction in symptoms: Several studies included in these reviews have shown that regular use of emollients can lead to a reduction in symptoms such as itching, redness, and inflammation associated with AD. This improvement in symptom control contributes to an enhanced quality of life for patients.

Prevention of flare-ups: Moisturizers play a role in preventing flare-ups of AD. By keeping the skin moisturized and maintaining its barrier function, they reduce the risk of skin irritation and exacerbations of the condition.

Adjunct to other treatments: Moisturizers are recommended as adjunctive therapy alongside other treatments, such as topical corticosteroids or calcineurin inhibitors. Their moisturizing properties can enhance the effectiveness of these anti-inflammatory treatments, and a sparing effect on the applied quantities of these anti-inflammatory treatments has been demonstrated in several instances.

Safety profile: Moisturizers generally have a favorable safety profile, making them suitable for long-term use, including in children and infants. This is particularly important in the management of a chronic condition like AD. A special attention should be given to the presence of potential allergens and irritants in the product.

Patient satisfaction: Patient satisfaction with emollient therapy is often high due to the relief it provides from itching and discomfort. This high satisfaction can contribute to better treatment adherence.

Search for authorized moisturizers for treatment of atopic dermatitis

The Regulatory Authorities' WHO-listed databases of medicinal drug products were used to identify moisturizers (ATC code D02A) for the treatment of AD. The approvals by national authorities are weighted high in our process to identify good quality products to be used in low-resource settings, see Tables 2A and 2B.

Carbamide-containing products identified

Three carbamide creams have been identified which are available internationally, where several generic versions are released. The **cream containing 5% carbamide is recommended** for inclusion on the EML and EMLc, as it fulfills the criteria for clinical evidence, Table 2A, also regarding the effect on skin barrier function and the prevention of eczema relapse. We **recommend against** inclusion of the other two urea-containing creams, where one was placed on the market already 1969 (10% urea+5% lactic acid) and the other in 1988 (4% urea+4% sodium chloride), Table 2B , see further **Evidence for comparative effectiveness of urea** below.

- **The recommended cream containing 5% urea was authorized by the MPA in 1997 for treatment of dry skin of different origin and for prevention of relapse of AD *(40)*.** It was shown in a randomized double-blind controlled (RCT) study to be milder to the skin than the cream containing 4% urea + 4% sodium chloride, as significantly fewer patients experienced temporary skin sensations, such as smarting, at days 15 and 31 in 48 patients with AD *(45)*. Furthermore, in a study on AD the cream containing 5% urea lowered TEWL whereas no

improvement in skin barrier function was observed from treatment with the cream containing 4% urea + 4% sodium chloride *(46)*. The 5% urea-based cream was also shown to improve skin barrier function and delay relapse of eczema and prolong the eczema-free periods in patients with AD *(84)* and in patients with hand-eczema *(41)*. The superiority of the urea-cream to a reference-cream in the risk-reduction of relapse was also proven in a multi-center, double-blind study *(43)*, see below

- **The cream we recommended against** contains **10% urea** in combination with 5% lactic acid as buffer (see Table 2B and Annex 2) and was authorized already in **1969** by the Medical Product Agency (MPA) in Sweden as medicinal product based upon clinical data on hyperkeratotic diseases (ichthyosis, AD and hand eczema) *(50-52)*. This product shows a satisfactory pH stability and notably also lowers TEWL in ichthyotic skin after treatment for 3 weeks *(54)* as well as in healthy forearm skin *(19)*. However, in a clinical study on 30 patients, also associated with AD, the patients preferred a cream with higher pH (about 6) to the acidic pH 3 due to less stinging sensations of this product *(53)*.
- **We also recommended against** the cream containing **4% urea** in combination with 4% sodium chloride (Table 2B) which was developed and authorized by MPA for treatment of dry skin in **1988**. It is a less acidic version of the original 10% urea and 5% lactic acid product and contains no lactic acid.

Carbamide combination products identified but not recommended

Two carbamide combination products are identified but not recommended for inclusion on the EML and EMLc due to a lack of clinical evidence related to the treatment of AD or a lack of clinical data on dryness and ambiguous results on barrier function, see Table 2B.

- Cream containing 5% carbamide in combination with the antipruritic/anesthetic compound polidocanol 3%) was authorized in 1998 for the treatment of pruritus, atopic eczema, dermatitis, and in scaling skin conditions where the antipruritic effect was required. The effectiveness of this product against chronic kidney disease-associated pruritus could not be proven in a recent phase IV, randomized, double-blind, controlled, parallel group trial versus a similar cream based on soft white paraffin 14.5%, light liquid paraffin 12.6% and anhydrous lanolin 1.0% *(85)*.
- Cream containing 2% urea in combination with 20% glycerol *increased* TEWL in a clinical RCT of 3 creams on the volar forearm *(9)*.

Other moisturizers and protective products identified

We recommend inclusion of the following two glycerol-containing products and recommend against inclusion of two propylene glycol products, see below and Tables 2A, 2B, and further **Evidence for comparative effectiveness of glycerol:**

- Cream containing glycerol 20%, which is authorized as a medicinal emollient for the treatment of dry skin and has been tested favorably in patients with AD *(39)*, and no negative effect on skin barrier function has been identified *(37)*. ***The inclusion on the EML and EMLc of the 20% glycerol is recommended.***
- Cream containing glycerol 15% combined with liquid and white soft paraffins as active ingredients (authorized as medicinal products). In a randomized, open-label study on children 2-6 years old of an emollient containing 15% glycerol + 2% liquid paraffin + 8% white soft paraffin, (not included in the systematic review), the frequency of flares, corticosteroid consumption as well as IGA and SCORAD scores were found to be lower

compared to no emollient use *(48, 49, 86)*. **We recommend the *product containing 15% glycerol + 2% liquid paraffin + 8% white soft paraffin for inclusion on the EML and EMLc***.

- Cream containing 20% propylene glycol combined with 4% lactic acid (for keratolytic treatment of hyperkeratotic dry skin. We **recommend against** the inclusion of this cream on the EML and EMLc, based upon lack of data on AD and the worsening of skin barrier function in ichthyosis with increased TEWL) *(55)*.
- Cream containing propylene glycol 20% (which is authorized as a humectant and contributes with some antimicrobial properties) as the single active ingredient. We **recommend against** the inclusion of this cream with propylene glycol as active substance on the EML and EMLc, as neither data on AD, nor on skin barrier function are available.

Search for literature on systematic reviews on moisturizers

In January 2024 a literature search was made in PubMed/Medline on the topic using the search terms “systematic review; atopic; topical; moisturizers; emollient” published during the last 15 years, covering clinical studies from 1981. In total 107 hits were retrieved out of which 7 systemic reviews were considered relevant and will be summarized and discussed in the present application. The priority to the systematic reviews and meta-analyses were given to the most comprehensive and high-quality reviews *(2-4)*. No efforts were made to reanalyze the data reported, but only to present the core information from the systematic reviews primarily by a copy-and-paste procedure.

Studies mentioned in the reviews but not completed and published (often industry sponsored), tends to suggest that these trials showed no, or marginal, benefit for the moisturiser under investigation *(3)*. Another remark relates to the use of non-invasive biophysical instruments. Skin hydration and barrier function can easily be measured as e.g. capacitance/conductance and TEWL (skin reaction), respectively, but where the impact on cream-residues on the outside of the skin may not have been taken into account, despite their nonspecific influence on the readings *(87-92)*. Handling of the instruments and cream-residues need careful design and interpretation, where the quote from Albert Kligman is still prevailing “a fool with a tool is still a fool”.

Reviews not included are, for example, those on antibiotics, antiseptics, oral treatment, newborns, hand eczema, and narrative reviews which described the role of moisturizers in eczema management but did not appraise the quality of the selected studies critically.

The following 7 systematic reviews were identified and used to summarize available evidence for effectiveness:

- Sidbury et al. 2023: Guidelines of care for the management of AD in adults with topical therapies *(4)*
- Nugroho et al 2023: The Efficacy of Moisturizers Containing Ceramide Compared with Other Moisturizers in the Management of Atopic Dermatitis: A Systematic Literature Review and Meta-Analysis *(93)*
- Tasker et al. 2020: What's new in atopic eczema? An analysis of systematic reviews published in 2018. Part 1: prevention and topical therapies *(94)*

- Fishbein et al. 2019 Systematic Review and Meta-analysis Comparing Topical Corticosteroids with Vehicle/Moisturizer in Childhood Atopic Dermatitis*(95)*
- Van Zuuren et al. 2017: Emollients and moisturizers for eczema: abridged Cochrane systematic review including GRADE assessments *(96)* and Van Zuuren et al. 2017: Emollients and moisturisers for eczema *(3)*
- Nankervis et al. 2016: Scoping systematic review of treatments for eczema *(5)*
- Lindh JD, Bradley 2015: Clinical Effectiveness of Moisturizers in Atopic Dermatitis and Related Disorders: A Systematic Review *(2)*

These published reviews give an excellent overview of the clinical benefits with the treatment of AD with emollients and moisturizers, **Table 3**. The 7 reviews were published between 2015 and 2023 and contain studies initiated from 1981, where some may still be ongoing and were not published at the time of the review.

The results from the systematic reviews are presented in **Annex 1**, where some parts of the publications are excerpted *in extenso*.

In general, the literature on AD treatment supports a strong recommendation for the use of moisturizers based on moderate certainty/evidence and our selection of carbamide and glycerol in defined cream bases as active substances is substantiated by the results, further descriptions of the findings below.

Table 3. Overview of the retrieved systematic reviews on the benefits of moisturizers on patients with atopic dermatitis.

Author, Year published	Sidbury et al 2023 ***(4)***	Nugroho et al 2023 ***(93)***	Tasker et al 2020 ***(94)***	Fishbein et al 2019 ***(95)***	Van Zuuren et al 2017 ***(3)***	Nankervis et al 2016 ***(5)***	Lindh et al 2015 ***(2)***
Focus	All treatment options	Ceramides	Studies indexed in 2018	TCS vs moisturizers	Moisturizers	New RCT	Moisturizers
Records screened	2161	2062	14	416	160	Not reported	595
No of studies analyzed	368, 11 on moisturizers	5	Not reported	13	77	> 50 RCT, 15 on moisturizers	48
Publication year of the studies	2012-2020	2012-2022	2018	1981-2013	Up to 2015	After 2000	Up to 2015 Jan
No of participants	500 on moisturizers	95	Not reported	2224	6603	Not reported	3262
Evidence on overall efficacy?	Yes	-	-	-	Yes	-	Yes
Evidence for carbamide	-	-	-	-	Yes	Yes	Yes
Evidence for glycerol	-	-	-	-	Yes	Yes	Yes

Evidence to support overall efficacy

Four extensive systematic reviews on moisturizers have been published since 2015. All of them conclude that the most important comparison, 'moisturizer vs. no moisturizer', showed moisturizers to reduce symptoms and severity of AD compared with no moisturizer *(2-5)*. The other three reviews had more narrow search strategies, Table 3.

Most moisturisers showed beneficial effects, but the authors did not find reliable evidence that one moisturiser was better than another. One publication concluded there was no clear evidence any of the more expensive preparations were superior to simple cheaper emollients *(5)*. Some authors mentioned the potential harmful effects from some emollients (e.g. to irritating and barrier weakening ingredients), albeit such effects were not confirmed in the reviews *(2, 5)*, see further information in other sections.

The first systematic review from **2015**, evaluated the effectiveness of moisturizers in the treatment of AD and related conditions, such as hand dermatitis, and/or ichthyosis vulgaris, using 48 studies and including 3262 patients *(2)*. The authors found that **the vast majority of studies indicate that moisturizers have beneficial effects on clinical symptoms** with moderate SCORAD reductions, decreased TEWL (range 0 to -12.2 g/m(2)h) and increased stratum corneum hydration (range +8 to +100%) *(2)*. The results from most of these studies were then evaluated once again in the later reviews presented in this application.

The second review from 2016 *(5)* summarised new RCT evidence on topical eczema treatments that did not fit into other categories, according to the authors, and which comprise moisturizers and other topical treatments. The authors mentioned that there is an increase in the number of emollient trials but the lack of reporting of methodological details was disappointing. Furthermore, the authors concluded there is no clear evidence that any of the more expensive preparations are superior to simple cheaper emollients, although some emollients such as aqueous cream (with SLS) may harm the skin barrier.

The authors found that topical treatments, such as [*Hippophae rhamnoides*, black seed oil, pill mask, rosmarinic acid, *Vitreoscilla filiformis*, shale oil, miltefosine, opiate receptor antagonist, carbohydrate-derived fulvic acid, raffinose, farnesol and xylitol, bacterial antigens, chamomille extract, heparin and levomenol, 15(R/S)-methyl-lipoxin A, *N*-acetyl-L-hydroxyproline, nalmefene hydrochloride monohydrate (SRD174)] were tested but none of the trials found any evidence of benefit compared with placebo or, in the case of licochalcone A, compared with hydrocortisone.

Studies on carbamide and glycerol are presented more in detail below, whereas trials on 13 other products are presented in Appendix 1.

The third review is the extensive Cochrane systematic review *(3)*, based on results from 77 clinical studies on eczema, including in total 6603 participants and many different types of analyses *(3)*.

In the Cochrane review, all moisturisers were compared to placebo, vehicle, or no moisturiser, providing many analyses, detailed in the publication. The most important ones are extracted *in extenso* below. **Moisturiser use yielded lower SCORAD indicating improvement compared no moisturiser** (three studies, 276 participants, mean difference (MD) -2.42, 95% confidence interval (CI) -4.55 to -0.28), but the minimal important difference (MID) (8.7) was unmet. Furthermore, moisturisers also led to **lower investigator-assessed disease severity** (12

studies, 1281 participants, SMD -1.04, 95% CI -1.57 to -0.51; high-quality evidence) and fewer flares (six studies, 607 participants, RR 0.33, 95% CI 0.17 to 0.62; moderate-quality evidence).

Participants also considered moisturizers effective in reducing eczema (five studies, 572 participants, RR 2.46, 95% CI 1.16 to 5.23; low-quality evidence) and itch (seven studies, 749 participants, SMD -1.10, 95% CI -1.83 to -0.38) than control. Participants in both treatment arms reported comparable satisfaction (three studies, 296 participants, RR 1.35, 95% CI 0.77 to 2.26; low-quality evidence). In Table 5, comparison no 6 is reported, where t**he number of patients experienced improvement is analysed**, Table 5.

Table 5. Analysis of the number of patients experienced improvement from treatment with moisturizers versus vehicle, placebo or no treatment, from *(3)* with permission.

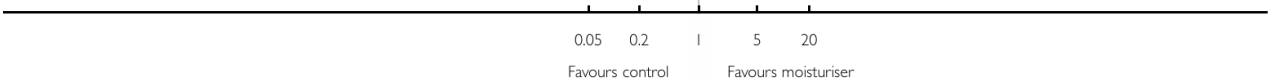
Analysis 6.1. Comparison 6 All moisturisers versus vehicle, placebo or no treatment (no moisturiser), Outcome 1 Number of participants that experienced improvement.

Review: Emollients and moisturisers for eczema

Comparison: 6 All moisturisers versus vehicle, placebo or no treatment (no moisturiser)

Outcome: 1 Number of participants that experienced improvement

Study or subgroup	Moisturiser n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Number of participants that experienced improvement (low risk of bias)					
Belloni 2005	8/15	2/15		13.2 %	4.00 [1.01, 15.81]
Nebus 2009	21/25	19/25		22.6 %	1.11 [0.84, 1.46]
Subtotal (95% CI)	**40**	**40**		**35.8 %**	**1.86 [0.41, 8.31]**
Total events: 29 (Moisturiser), 21 (Control)					
Heterogeneity: Tau^2 = 0.96; Chi^2 = 4.75, df = 1 (P = 0.03); I^2 =79%					
Test for overall effect: Z = 0.81 (P = 0.42)					
2 Number of participants that experienced improvement (unclear risk of bias)					
Boguniewicz 2008	58/72	7/70		19.3 %	8.06 [3.95, 16.42]
Lod n 2002	57/66	46/66		23.0 %	1.24 [1.03, 1.49]
Subtotal (95% CI)	**138**	**136**		**42.4 %**	**3.11 [0.25, 38.71]**
Total events: 115 (Moisturiser), 53 (Control)					
Heterogeneity: Tau^2 = 3.25; Chi^2 = 47.06, df = 1 (P<0.00001); I^2 =98%					
Test for overall effect: Z = 0.88 (P = 0.38)					
3 Number of participants that experienced improvement (high risk of bias)					
Abramovits 2008	108/145	18/73		21.8 %	3.02 [2.00, 4.56]
Subtotal (95% CI)	**145**	**73**		**21.8 %**	**3.02 [2.00, 4.56]**
Total events: 108 (Moisturiser), 18 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.26 (P < 0.00001)					
Total (95% CI)	**323**	**249**		**100.0 %**	**2.46 [1.16, 5.23]**
Total events: 252 (Moisturiser), 92 (Control)					
Heterogeneity: Tau^2 = 0.63; Chi^2 = 75.73, df = 4 (P<0.00001); I^2 =95%					
Test for overall effect: Z = 2.34 (P = 0.019)					
Test for subgroup differences: Chi^2 = 0.38, df = 2 (P = 0.83), I^2 =0.0%					



Topical active treatment using topical corticosteroids or topical calcineurin inhibitors combined with moisturizer was more effective than active treatment alone in reducing investigator-assessed disease severity (three studies, 192 participants, SMD -0.87, 95% CI -1.17 to -0.57; moderate-quality evidence) and flares (one study, 105 participants, RR 0.43, 95% CI 0.20 to 0.93), and was preferred by participants (both low-quality evidence).

There were fewer flares with moisturisers (two studies, 87 participants, RR 0.40, 95% CI 0.23 to 0.70), time to flare was prolonged (median: 180 versus 30 days), and less topical corticosteroids were needed (two studies, 222 participants, MD -9.30 g, 95% CI -15.3 to -3.27). The rate of flares was reduced (hazard ratio 3·74, 95% CI 1·86-7·50). **Adding moisturizers to topical anti-inflammatory treatment was more effective than anti-inflammatory treatment alone** and resulted in fewer flares. For example, more flares were reported with moisturizer alone than when combined with twice-weekly fluticasone propionate (risk ratio 2·17, 95% CI 1·55-3·11) *(3)*.

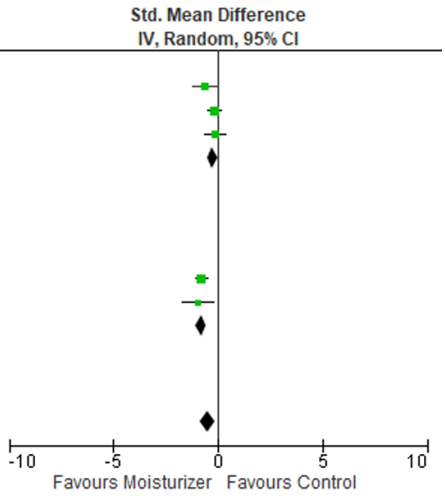
The fourth and most recent systematic review **from 2023,** published by the AAD, also concluded that **moisturizers reduced signs, symptoms, and inflammation in AD, they improved AD severity and increased time between AD flares** *(4)*. AD severity was reduced with the use of moisturizers as measured by SCORAD and the EASI (SMD of 0.51, 95%, CI: 0.17-0.85), along with improvement using self-assessment, see analyses 1a and 1b, respectively, in Table 6. The change from baseline in itch and the number of patients experiencing a flare are shown in analysis 1c and 1d, respectively.

The AAD also noted that topical moisturizers **target xerosis by minimizing TEWL and improve SC hydration** and are integral to nearly all AD management plans, as they are typically utilized as part of a comprehensive regimen with pharmacologic treatments but may also be used as monotherapy in mild cases. **The AAD strongly recommended the use of moisturizers for adults with AD** but could not recommend a particular moisturizer or active ingredient in an emollient *(4)*.

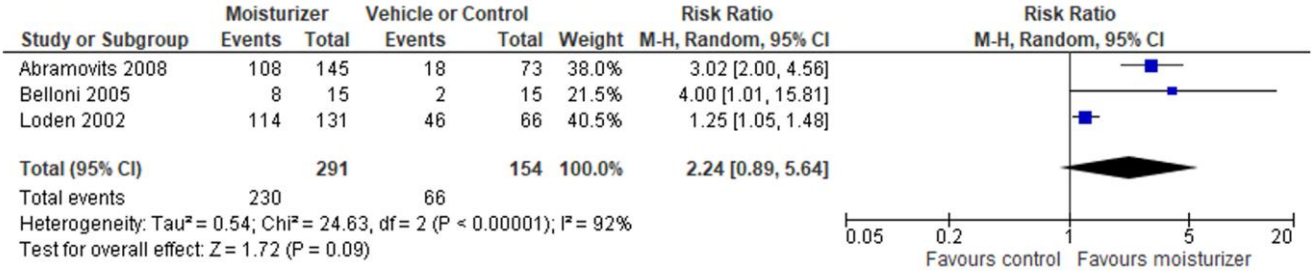
Table 6. Online supplement to the "Guidelines of care for the management and treatment of atopic dermatitis in adults with topical therapies" (available via Mendeley at https://data.mendeley.com/datasets/fmkr7fwx9j/2) , reproduced with permission from ***(4)***.

Analysis 1a. Change in disease severity as assessed by investigators (SCORAD & EASI)

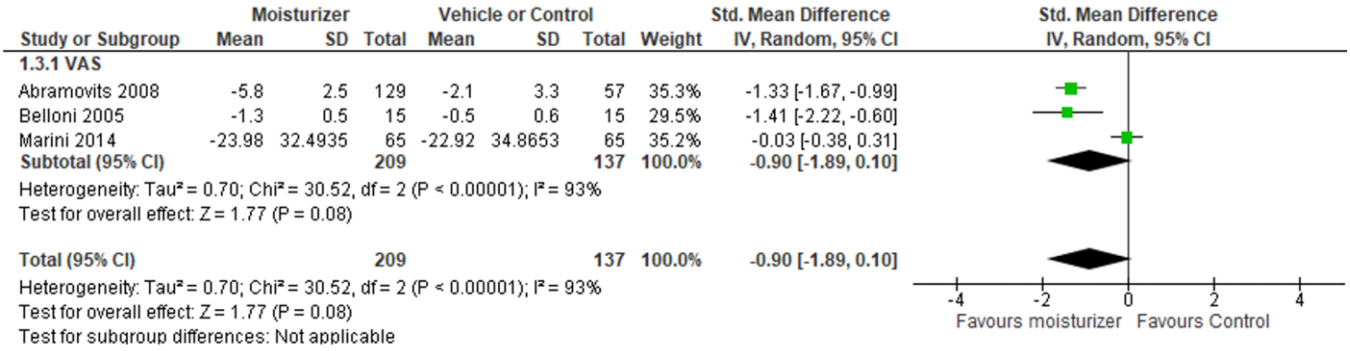
Study or Subgroup	Moisturizer Mean	SD	Total	Vehicle or Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 SCORAD								
Breternitz 2008	-1.1	1.57	24	0	1.83	24	16.8%	-0.63 [-1.22, -0.05]
Marini 2014	-3.74	3.4707	65	-3.1	3.4304	65	24.9%	-0.18 [-0.53, 0.16]
Tan 2010	-12.67	7.7	30	-11.69	7.7	30	19.1%	-0.13 [-0.63, 0.38]
Subtotal (95% CI)			**119**			**119**	**60.8%**	**-0.26 [-0.52, 0.00]**
Heterogeneity: Tau² = 0.00; Chi² = 2.05, df = 2 (P = 0.36); I² = 2%								
Test for overall effect: Z = 1.94 (P = 0.05)								
1.1.2 EASI								
Abramovits 2008	-4.38	3.94	145	-0.76	5.52	73	26.9%	-0.80 [-1.09, -0.51]
Belloni 2005	-4	3.9	15	-0.7	2.6	15	12.3%	-0.97 [-1.73, -0.21]
Subtotal (95% CI)			**160**			**88**	**39.2%**	**-0.82 [-1.09, -0.55]**
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%								
Test for overall effect: Z = 5.90 (P < 0.00001)								
Total (95% CI)			**279**			**207**	**100.0%**	**-0.51 [-0.85, -0.17]**
Heterogeneity: Tau² = 0.09; Chi² = 10.92, df = 4 (P = 0.03); I² = 63%								
Test for overall effect: Z = 2.97 (P = 0.003)								
Test for subgroup differences: Chi² = 8.52, df = 1 (P = 0.004), I² = 88.3%								



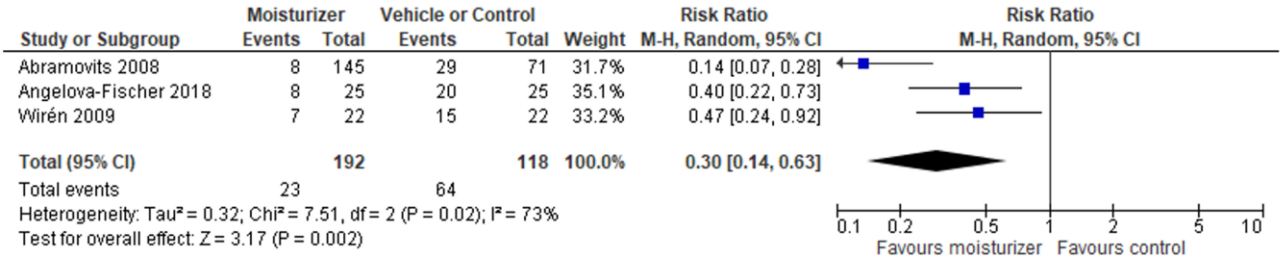
Analysis 1b. Number of participants who experienced improvement (self-assessed)



Analysis 1c. Change from baseline in itch.



Analysis 1d. Number of participants who experienced a flare.



The three more narrow reviews, such as e.g. **Fishbein** et al **2019** *(95)* aimed to determine the safety and efficacy of topical corticosteroid versus vehicle/moisturizer in children under 2 years old using results from 12 RCT on 2224 participants. The authors concluded **that topical corticosteroids tended to being more effective and equally safe to vehicle/moisturizers**, but generalizability is limited given the dearth of well-designed studies focused on children under 2 years.

Tasker et al. 2020 *(94)* gave an annual update and summarized results published or indexed in 2018. The review focused mainly on oral treatment during pregnancy and in newborns and no general opinion was expressed on the benefit with moisturizers in AD. **Nugroho** et al. 2023 *(93)* did not express any general view on the benefit of moisturizers for treatment of AD, instead the review focused on ceramides and found a significant difference in SCORAD in favour to the moisturisers containing ceramide (2 studies), but no differences in TEWL were detected (3 studies).

Evidence for the moisturizers recommended for EML listing emollients

Our conclusion to recommend carbamide and glycerol in moisturizers is supported and well-suited as a first-line choice in patients with AD, based upon the retrieved literature. Furthermore,

these substances are described in pharmacopoeias and are authorized by national authorities to be used in medicinal products, Table 2A.

The Cochrane review included four studies (362 participants (adults)) comparing urea-containing moisturizers versus vehicle, placebo or no treatment, and three studies (409 participants (adults and children)) comparing glycerol-containing moisturizers versus vehicle or placebo, and concluded that **urea and glycerol containing creams work better than their controls (vehicle, placebo or no moisturizer) according to both participants and physicians**, whereas the evidence for many other proposed preparations were less certain *(3)*.

In the systematic review by Lindh and Bradley *(2)* it was also found that the clinical effectiveness appears **most well-documented for preparations containing urea and glycerol** than, for example, propylene glycol, lactate, ceramide, and aluminum chlorohydrate *(2)*. Lindh and Bradley *(2)* also noted that studies on urea were less often associated with a high risk of bias compared with studies on glycerol *(2)*.

Evidence for comparative effectiveness of urea:

Cochrane noted that there is **low to moderate quality** evidence that **urea**-containing creams are more effective than no moisturiser, placebo or vehicle (based on both investigator and participant assessments) *(3)*.

Urea-containing cream **improved dryness (investigator-assessed)** more frequently (one study, 128 participants, RR 1.40, 95% CI 1.14 to 1.71; moderate-quality evidence) with fewer flares (one study, 44 participants, RR 0.47, 95% CI 0.24 to 0.92; low-quality evidence), but more participants in this group reported adverse events (one study, 129 participants, RR 1.65, 95% CI 1.16 to 2.34; moderate-quality evidence). Four studies evaluated urea-containing creams.

Participants reported skin improvement more frequently with urea-containing cream than placebo (one study, 129 participants, RR 1.28, 95% CI 1.06 to 1.53; low-quality evidence), with equal satisfaction between the two groups (one study, 38 participants, low-quality evidence).

Efficacy was confirmed by one study, at low risk of bias, conducted over 180 days, that showed that **barrier-strengthening moisturiser with 5% urea reduced the number of participants who experienced a flare, and increased time to flare** in comparison to the reference cream. The Cochrane review also reported that a barrier-strengthening moisturiser with 5% urea *(43)* **reduced the number of participants** who experienced a flare, and increased time to flare in comparison to the reference cream (one RCT, 172 participants (adults), with **low risk of bias**) *(3)*. Following a stabilisation phase in which active treatment (mometasone) was used until the eczema was (almost) cleared, patients were randomized to 5% urea cream or reference cream for the maintenance phase. During the maintenance phase of 180 days without active treatment, the primary efficacy endpoint was time between randomization and experiencing a flare. In both the full analysis set, and the per protocol set, the risk of flare of was significantly reduced in the 5% urea cream group). At the end of the 180-day maintenance phase, 21/87 of the participants in the urea group had not experienced a flare, compared to 8/85 in the reference group (RR 2.56, 95% CI 1.20 to 5.47; P = 0.01; NNTB = 7, 95% CI 3 to 26). The median time to flare was 22 days in the urea group compared to 15 days in the reference group. At day 180, 66/87 (75.8%) in the urea group had a flare versus 77/85 (90.1%) in the reference group, which corresponds to an absolute risk reduction of flare of 14.0% and a relative risk reduction of 15.6%

(3). Sidbury et al (AAD) *(4)* also reported reduced risks for flare from treatment with urea in the Wiren et al. 2009 study *(42)*.

In addition, the mean score (and SD) using the EQ-5D 5-item instrument, was 0.945 (0.137) at the beginning of the maintenance phase and 0.951 (0.093) at end of study in the urea group, but this score dropped to 0.881 (0.154) in those with a flare *(3)*. In the reference group, the score at the start of the maintenance phase was 0.931 (0.135), and at the end of the study and during flare, it was 0.935 (0.136) and 0.851 (0.152), respectively. These scores indicate that the quality of life remained relatively stable during the eczema free periods but decreased during a flare *(3)*.

Lindh and Bradley *(2)* also compared different concentrations of urea back-to-back in two studies *(2)*, both including patients with AD *(97, 98)*. In the first study (100 participants), urea in concentrations of 5 and 10 % had very similar effects on SCORAD (-19.76 and -19.23 %, respectively, p=0.37) *(97)*. However, cosmetic acceptability was rated significantly higher for the 5 % preparation (p=0.001). This study had a relatively high drop-out rate (16 % for 5 weeks), which could have introduced bias since the analysis was performed per protocol, i.e., disregarding patients who failed to fulfil study participation. In the second study (57 participants), urea 10 % had a significantly better effect on eczematous eruptions (p=0.01) and skin dryness (p<0.05) compared with urea 5 % *(98)*. However, the high- and low-concentration preparations also differed by their content of lactic acid and propylene glycol, respectively.

Lindh and Bradley also noted *(2)* that the 5%-urea containing cream **delayed time to relapse** of eczema in the Wiren et al. study *(42)*.

Nankervis et al *(5)* also commented on the significant findings in delay in time to relapse, which was > 6 months for the urea group compared with 30 days when using no treatment in the Wiren study *(42)*, with a relative risk reduction of 53% and number needed to treat of 2.8. Furthermore, the study by Bissonnette *(97)* did not find a statistically significant difference in eczema severity between the urea cream (5%) and the urea lotion (10%) after 42 days of treatment (19.76% vs. 19.23% reduction in mean SCORAD scores). The trial report states that the urea cream (5%) had better cosmetic acceptability than the urea lotion (10%).

Evidence for comparative effectiveness of glycerol:

The Cochrane review noted that there is **moderate to high quality** evidence that **glycerol**-containing moisturisers are more effective than 'vehicle' or placebo (investigator and participant assessments), but the minimal important difference (MID) was not met *(3)*.

Three studies assessed glycerol-containing moisturiser versus vehicle or placebo. **More participants in the glycerol group noticed skin improvement** (one study, 134 participants, RR 1.22, 95% CI 1.01 to 1.48; moderate-quality evidence), and this group saw **improved investigator-assessed SCORAD** (one study, 249 participants, MD -2.20, 95% CI -3.44 to -0.96; high-quality evidence), but MID was unmet. Participant satisfaction was not addressed. The number of participants reporting adverse events was not statistically significant (two studies, 385 participants, RR 0.90, 95% CI 0.68 to 1.19; moderate-quality evidence).

Sidbury et al (AAD) also concluded that moisturizers improve AD severity (3 studies, 445 participants), see Analysis 1b in Table 5 *(4)*, where 20% glycerol was used in the Lodén 2002 study *(39)* and a moisturizer containing the non-authorized substance glycyrrhetinic acid in the Abramovits and Belloni studies *(99, 100)*.

After publishing the systematic reviews, two additional studies of glycerol 15% was found based on data from one study *(48, 49)*. This was a randomized, open-label study comparing 15% glycerol to reference moisturizer (with glycyrrhetinic acid) or no emollient use in 335 children 2-6 years old with AD*(48)*. At inclusion, flare severity was moderate or mild (IGA = 3 or 2) in almost all patients (74.0% and 23.6%), and at randomization, all flares were clear or almost clear (IGA = 0 or 1) *(48)*. After 12 weeks of treatment, SCORAD score was reduced by 5.28 points in the glycerol group and by 3.36 points in the reference emollient group compared with the no emollient group (+4 points; P < 0.001 in both emollient groups vs. no emollient group). At the end of the study, the percentage of patients in complete remission (i.e. without a new flare over the treatment period) was higher in the glycerol group (59.5%) and reference emollient (44.3%) groups than in the no emollient group (29.8%; P < 0.001) *(49)*. Fewer patients treated with 15% glycerol required any corticosteroids or immunosuppressants (23.6%) than patients with no emollient (43.3%) at 12 weeks *(48)*.

General summary of safety

Moisturizers are rarely associated with health hazards, although they may be used on large body areas over a large part of the human life span. More commonly encountered reactions are various forms of skin discomfort from moisturizers, since virtually any substance can cause skin reactions in sensitive areas in some individuals. AD patients with impaired barrier function are particularly at risk for adverse skin reactions.

The active substances in the recommended moisturizers are approved to be used in food and are also found in the body. Carbamide (urea, E 927b) is a physiological substance occurring in human tissues, sweat, blood, and urine, as the main nitrogen containing degradation product of protein metabolism. Blood concentrations range from 200 to 400 mg/L (54) and approximately 20–35 g of urea is excreted in human urine per day. Glycerol (E 422) is used as a humectant, sweetener, solvent, plasticizer and a lubricant in a variety of consumer products *(101)*. The alcohol is a clear, colourless, hygroscopic syrupy, approximately 0.6 times as sweet as cane sugar. Glycerol is produced most by hydrolysis or saponification of fats or oils which involves breaking down triglycerides into glycerol and fatty acids.

Data from National Authorities on undesirable effects

Possible side effects

The frequency and severity of the adverse effects of the proposed medicines are expected to be the same as those recognized by e.g. the medical authority in the EU, such as the creams with 50 mg/g urea, 150 mg/g glycerol and 200 mg/g glycerol.

The official information from the authorities states that “like all medicines, the cream can cause side effects, although not everybody gets them”. No serious adverse effects are mentioned but it is common that local, transient sensation of smarting, itching, stinging and redness, expressed as follows:

- **Urea 5%**: The cream can give transient, local sensation of burning and heat (experienced by more than 1 out of 100 users). The face is most sensitive.
- **Glycerol 15%**: Uncommonly reported side effects (occurring in less than 1 in 100 patients) are: hives, itching, redness, eczema, rash and reactions at the application site (irritation, redness, pain or itching). Other effects of unknown frequency (cannot be estimated from the

available data) may occur such as eczema at the application site and burning sensation of the skin.
- **Glycerol 20%**: Transient smarting, itching, stinging and redness.

Clinical particulars

Contraindications for use are: Hypersensitivity to the active substance or any of the excipients.

Special warnings and precautions for use: Risk of systemic effects has not been observed in clinical studies of these medicinal products.

Pregnancy and lactation: The creams can be used during pregnancy and lactation

The 20% glycerol cream (Miniderm) contains cetostearyl alcohol, which may cause local skin reactions (e.g. contact eczema). It also contains ethyl and methyl parahydroxybenzoate, which may cause allergic reactions (possibly delayed).

Interaction with other medicinal products and other forms of interaction: formal interaction studies have not been performed.

Effects on ability to drive and use machines: There is no indication that those creams have any effect on the ability to drive or use machines.

Consideration of the potential for and consequences of inappropriate use or use outside the proposed indication.

There are no data in the literature suggesting that the data on carbamide or glycerol in the treatment of dry skin are limited to certain sub-groups of the populations, due to any intrinsic or extrinsic factor. No interactions with other medicinal products or substances are expected. No systemic influences on the body will occur.

Except for lack of efficacy and delay in appropriate management, similar benign skin side effects are expected.

Information on any variation in safety that may relate to health systems or patient factors.

There is limited published information on this issue. As discussed for sub-Saharan Africa, the prominent role of traditional healers is the cause of superimposed morbidity due to herbal therapies given topically or orally, which may complicate the attribution of side effects *(57) (102)*. In addition, the quality or storage of over the counter skin care products used by patients may not be optimal and may increase the risk of side effects *(57, 102)*.

Information on any warning or safety issues identified by regulatory authorities (e.g., black box warning, drug safety alerts etc).

The European Commission guideline on excipients states that the presence of certain excipients in the cream should be alerted in the sections **Special Warnings** and **Precautions** in the package leaflet *(103)*, such as e.g.:

- Parahydroxybenzoates and their esters, such as ethyl and methyl parahydroxybenzoate should be labelled: May cause allergic reactions (possibly delayed).
- Propylene glycol may cause skin irritation. Do not use this medicine in babies less than 4 weeks old with open wounds or large areas of broken or damaged skin (such as burns) without talking to your doctor or pharmacist. Limit 50 mg/kg/day
- Stearyl alcohol, cetostearyl alcohol including Cetyl alcohol: May cause local skin reactions (e.g. contact dermatitis)

Literature evidence for safety

Bhanot et al. *(104)* searched MEDLINE from inception (1946) to May 2022. Inclusion criteria were RCTs of moisturizers/ emollients used as a leave-on treatment (as the intervention or control) in adults or children with eczema. Exclusion criteria were non-RCTs; patients with other diagnoses included use of emollient as bath additives, soap substitutes or as preventative, and not published in English.

24 papers reported on adverse events with 29 different moisturizers (3 containing urea, 5 containing ceramide, 4 containing glycerol, 4 were herbal and 13 contained "other" ingredients). Interpretation of the results and comparison of the moisturizers were difficult due to poor reporting and missing data. Many publications contained no data at all on adverse events, and no study reported serious treatment-related adverse events for any moisturizer. The proportion of participants in the studies experiencing treatment-related adverse events varied between 2 and 59%. The most common adverse events were skin related and often mild. The range of participants experiencing non-treatment-related adverse events varied between 4 and 43%. The authors conclude that clinicians and patients can be reassured that the moisturizers studied appear to be generally safe to use. Those results are comparable to the Cochrane review *(3)* which reported that the relative risks of an adverse event from all moisturizers was 24 per 100 (95% confidence interval 19–30) compared with 23 per 100 with vehicle, placebo or no moisturizer (10 RCTs, 1275 participants, follow-up range from 4 weeks to 6 months) but that there were more adverse events associated with urea-containing creams (65 per 100 participants in 1 RCT in which 129 participants were compared with placebo) and oat-containing moisturizers (9 per 100 participants in 1 RCT in which 173 participants were compared with no moisturizer). This is understandable for urea and lactic acid-based formulations which are more prone to temporary reactions than high lipid content and inverse emulsions, but that most individuals will tolerate.

Fragrances and preservatives are identified as the major sensitizers in topical formulations. Humectants, emulsifiers and oils hardly ever cause contact allergy *(105)*. Lanolins are sometimes proposed to be a frequent cause of contact allergy, but this is believed to be due to inappropriate testing conditions leading to false-positive reactions *(105)*. The most common adverse reactions to moisturizers are temporary sensory reactions or subjective sensations (no signs of inflammation) immediately after application. Humectants, such as lactic acid*(106)*, urea *(107, 108)*, pyrrolidone carboxylic acid (PCA) *(109)* and preservatives, like benzoic acid *(109)* and sorbic acid *(108)* cause such subjective sensations, where the type of formulation also may influence the degree of reactions *(110)*.

Evidence to support recommendation against certain moisturizers

The present application recommends against listing of moisturizers if they had not been studied on AD and are not supported by evidence in the 7 systematic reviews assessed, or in the supplementary data retrieved e.g. Boralevi et al. 2014 *(86)* and Tiplica et al. 2017, 2018 *(48, 49)*.

We also recommend against moisturizers containing barrier-weakening substances, such as the potentially most well-known SLS used in aqueous cream BP. The Cochrane review *(3)* alerted the readers about barrier-weaking effects from this surfactant and referred to studies stating that aqueous cream BP (or other leave-on moisturisers containing SLS) should not be used as a leave-on moisturiser in eczema, as this has been shown to have a negative impact on the skin barrier *(12, 111)*. We therefore recommend against the inclusion of moisturizers containing

barrier weakening substances, such as SLS, as it weakens skin barrier in people with a history of AD *(12)* and exacerbates AD symptoms *(111)*. Treatment induced higher TEWL and a thinner stratum corneum *(112)*.

In addition, the Cochrane review mentioned that some recent studies have questioned or discouraged the use of oils as they can damage the skin barrier or impair skin barrier maturation in neonates *(10, 113, 114)*. Several vegetable oils impart an elegant texture to moisturizers but provide no scientifically proven benefit but instead may damage the skin *(25)*.

Therefore, we also recommend against the inclusion of moisturizers containing olive oil and high concentrations of oils rich in oleic acid. This is based upon differences between the impact of olive oil and sunflower oil on the skin, where treatment with olive oil for 4 weeks significantly reduced stratum corneum integrity and induced mild erythema and was suggested to exacerbate existing AD *(10)*, whereas sunflower seed oil preserved stratum corneum integrity and did not cause erythema in the volunteers *(10)*. Olive oil releases the penetration enhancer oleic acid in the skin upon hydrolysis, which is the main fatty acid in olive oil *(115)*. Oleic acid is suggested to induce stratum corneum lipid fluidization and phase separation of the lipids in the barrier layer *(115, 116)*.

Not only certain oils, but also excipients such as emulsifiers, solvents and penetration enhancers are advocated to potentially induce subclinical irritation and to promote outbreak of eczema *(9, 10, 12, 25, 111, 117-121)* and aggravate AD *(87, 122-124)*, whereas humectants, such as carbamide and glycerol are reported to strengthen the skin barrier in AD skin and delay relapses of eczema *(42, 43)*. Certain antimicrobial alcohols and glycols, such as the pentylene glycol and ethylhexylglycerin are reported to act as penetration enhancers *(117)*.

Not only sensitive AD skin, but also healthy skin may suffer from a weakened skin barrier function and react stronger to environmental stimuli (allergens, surfactants, solvents) after the use of barrier-damaging creams *(19, 120, 125, 126)*.

We found no evidence to support the general use of certain fatty acid creams as they can impair skin barrier maturation in neonates *(10, 113, 114)*. In addition, similar fatty creams without humectants have been found to weaken healthy skin barrier function and potentially promote eczema *(8, 120, 121)*. Thus, they are not proposed for inclusion.

On the other hand, petrolatum is reported to penetrate into the outermost layer of delipidized stratum corneum and to reduce TEWL *(127)*. Petrolatum is used in the recommended glycerol creams.

We also do not propose listing urea-containing creams with high pH. Such creams may threaten the “acid mantle” of the skin, which may facilitate growth of barrier-damaging microorganisms *(Staphylococcus aureus*). They may also contain too high amounts of irritating ammonia. It is also worth remembering that improvement of skin barrier function in urea-treated skin occurs in parallel with enhanced expression of antimicrobial peptides in the skin *(128)*. It is also known that not all urea-creams improve skin barrier function *(7)*. The reason to the failure is not fully understood but is likely due to too low concentration of urea, and/or potential damaging effects from excipients or decomposition products in the cream *(9)*.

At last, we recommend against the use of moisturizers containing substances which are not authorized for use in medicinal products as an active substance or as an excipient, despite use in several studies and being promoted internationally. Price constraints may also limit their

suitability. For example, among the potential active substances cited in the systematic reviews, extracts from the roots of Glycyrrhiza species and ceramides are noted. These substances (e.g. glycyrrhetinic acid and licochalcone A) have chemical structures related to cortisone, and are described as having anti-inflammatory and be involved in anticancer activity *(129, 130)*. Ceramides are complex and large lipophilic substances *(131)*, which limit their diffusion in the stratum corneum *(132)*, appears to have no superior effect on skin barrier function, and are also linked to cannabinoid-induced apoptosis *(133)*. Greater scientific clarity of the chemistry of ceramides is also requested in the dermatological literature to allow comparison of different publications of products containing ceramides *(131)*.

Conclusions: risks/benefits of the selected products

The therapeutic benefit of the recommended moisturizing creams containing carbamide or glycerol as active ingredients for treatment of AD is well established. The products have been authorized through national or mutual recognition procedures by competent European authorities for decades. Furthermore, their clinical effectiveness is demonstrated and is openly published and judged positively for scientific quality by different expert groups.
Their benefits in relieving the symptoms of AD clearly outweigh their risks, especially when skin barrier function improves and the time to relapse of eczema is prolonged.

The active ingredients are normally occurring metabolites in the body and topical treatment will not influence their amount in the body. The excipients are well-established substances in medicinal products, as well as in consumer products, such as cosmetics and food. The majority complies with the EU pharmacopoeia.

It is well-known that all topically applied products may cause temporary skin reactions in sensitive skin, especially in patients with broken skin barrier, and some excipients may also cause irreversible skin reactions, such as e.g. skin allergy. The product labelling, and other information materials, will demonstrate that the risk reduction measures are adequate.

In conclusion, the clinical effectiveness of the recommended moisturizing creams justifies their use in the treatment of AD. The creams have a clearly positive benefit / risk profile within the context of the intended indication according to current state of the art in the medical fields concerned and according to available medical alternatives.

Annex 2 includes a discussion of formulation issues based on risk/benefits/costs.

Assessment of applicability of the available evidence across diverse populations and settings

Several studies have identified variations in the prevalence of AD in different ethnic groups, where for example higher prevalence and a greater burden of pruritus in black children compared to white children are reported *(134-138)*. Differences in in skin barrier properties (e.g. TEWL, skin lipid levels, pH) are also observed between different ethnic populations, but the findings are still inconsistent and their clinical relevance have not been established *(134)*.

Only one study was found looking at applicability and evidence in the sub-Saharan African population *(139)* of children and adults:

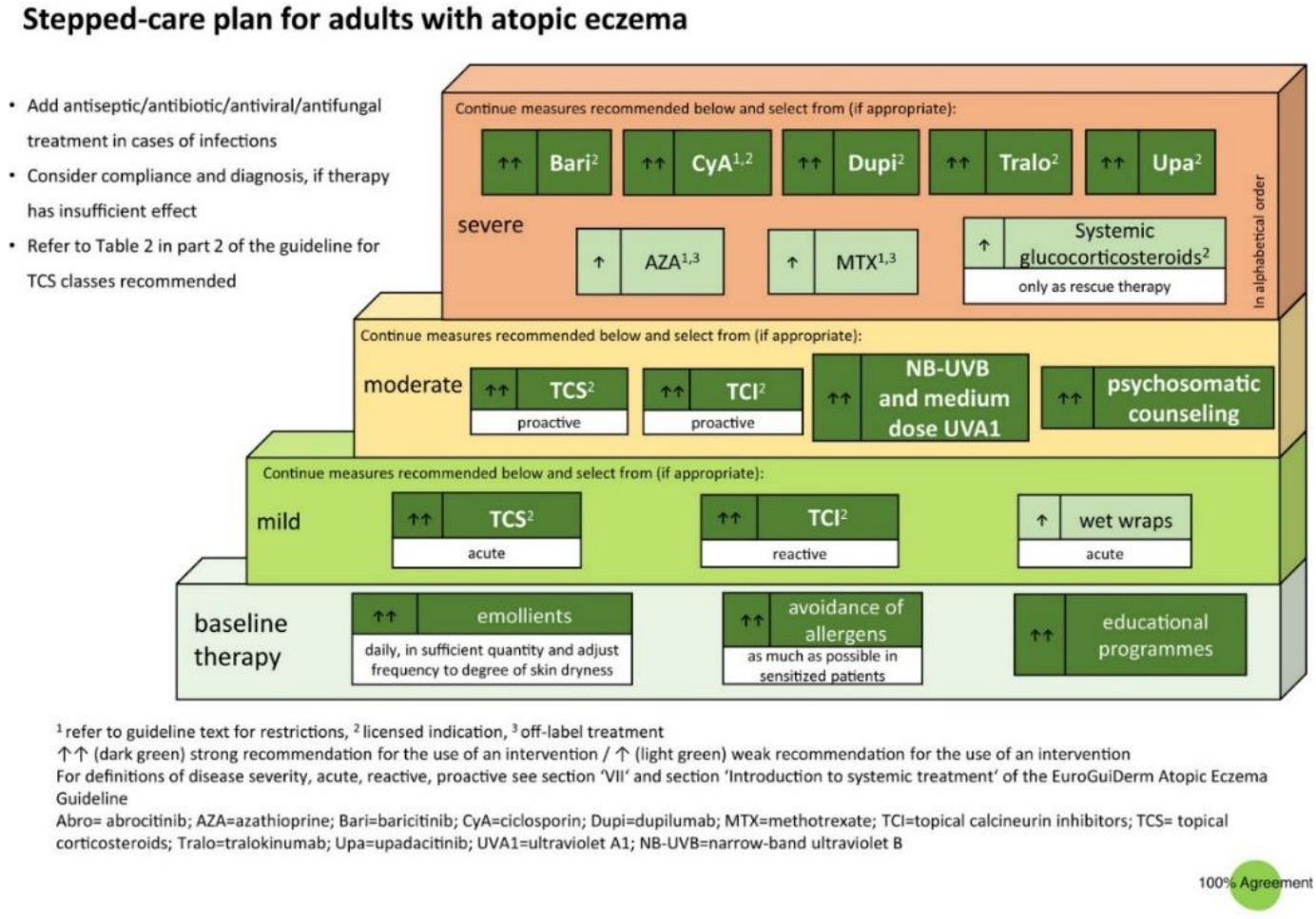
The observational study “Xerafrica” was conducted by dermatologists in seven sub-Saharan countries to assess under real-life conditions the evolution of xerosis in patients with (about 1/3) and without AD after an 8-week treatment with a 15% glycerol-based emollient. Patients were children over 3 years or adults. Secondary objectives were to assess pruritus, improvement in symptoms, quality of life, satisfaction, and tolerance. An analysis of 185 patients was made. After 8 weeks of emollient treatment, the relative reduction of the “Scaling Roughness Redness Cracks” (SRRC) score was 83.9% and 80.4% in children and adults, respectively. The effect was significantly stronger when topical steroids were co-prescribed with the emollient and in patients with co-dermatosis. To a lesser extent, the effect of emollient was also observed at week 4. Similarly, pruritus and quality of life strongly improved during follow-up. Skin lesions improved in almost all patients, with a high level of satisfaction noted by both dermatologists and patients.

Section 9: Summary of recommendations in current clinical guidelines

WHO guidelines for the treatment of AD are not available.

The latest current EU guideline recommends moisturizers as a first-line treatment for all ages, including infants and children *(140)*, Fig 3. This is in agreement with all major published guidelines *(4, 73)*, which recommend the use of emollients as a first line of treatment of AD, also including Africa and the Middle East *(61)*. Nonpharmacological treatment primarily focuses on adequate skin care, with regular moisturizer and emollient use to prevent dryness, strengthen skin barrier function and decrease risks for eczema. Their use belongs to the most prescribed products in dermatology and is emphasized also when the eczema is cleared *(61, 141-143)*. To reduce the risk of skin allergy fragrance-free and hypoallergenic emollients are recommended. The choice of the product may depend on the patient's skin type and personal preferences.

Education of patients and caregivers about proper emollient application techniques is emphasized in the current guidelines since adherence to the emollient regimen is essential for symptom management and skin barrier repair. In all settings, skill levels of healthcare providers need to be strengthened to provide basic care education *(57) (102)*. AD is a chronic condition, and emollients should be used consistently over the long term, even during periods of remission, to help prevent flare-ups and maintain skin hydration. Emollients are most often used in combination with other treatments for AD, such as topical corticosteroids or calcineurin inhibitors. As mentioned above in **Section 6,** the applicability of current western guidelines to low-resources southern countries is questionable. Concerning moisturizers their cost prevents them from being routinely used as a baseline therapy.



Symbols	Implications (adapted from GRADE [1])
↑↑	We believe that all or almost all informed people would make that choice.
↑	We believe that most informed people would make that choice, but a substantial number would not.
0	We cannot make a recommendation.
↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.
↓↓	We believe that all or almost all informed people would make a choice against that choice.
	No recommendation.

Figure 3: Outline of the stepped approach for the treatment of adult atopic dermatitis including moisturizer as a first line *(140)*.

Section 10: Summary of available data on comparative cost and cost-effectiveness

The African Atopic Dermatitis Guidelines Working Group is made up of African dermatologists working in Africa with a special interest in AD. All are members of the African Society of Dermatology & Venereology (ASDV) by their nationality and location of practice, and a link has been established with the ISAD to make a survey on the accessibility of emollients in the management of AD in Sub-Saharan Africa.

A pilot survey was carried out by this group between October 2023 and April 2024. The results were presented at the 2024 scientific congress of the ASDV in Tunisia in April 2024. Data was gathered from 12 (22%) countries across the continent with a skewing to West Africa and fewer representation from North Africa. Countries represented include Benin, Burkina Faso, Cameroun, Cote d'Ivoire, Democratic Republic of Congo, Madagascar, Mali, Mauritania, Nigeria, Senegal, South Africa and Rwanda.

AD is prevalent in all countries and all face difficulties procuring emollients. Traditional emollients such as shea butter and coconut oil were available in > 50% of the countries however there are inconsistencies in the quality. Prescribed emollients for the management of AD in all countries were imported. The most prescribed emollients were Vaseline Petroleum jelly, followed by Dexeryl (***discussed in this application***) and creams such as Topicrem, Cerave, Lipikar, and Neutraderm brands. While these are available, they are not easily accessible due to the prohibiting cost for the average citizen.

At the time of compiling this data, the less expensive product (***ointment, not discussed in this application***), vaseline petroleum jelly 450 ml tub costs an average of N3,320 ($2.25) in Nigeria, R64.99 ($3.54) in South Africa and Ar 20,000 ($ 4) in Madagascar. The monthly minimum wages (in USD $) in the three countries are $20, $99 and $22 respectively for the lowest cadre of workers such as domestic staff. According to statista.com as of 2022, Morocco was the African country with the highest estimated minimum gross monthly wage, standing at 285 U.S. dollars. It was followed by South Africa at 248 U.S. dollars and Gabon at 240 U.S. dollars. Among the selected nations, only three countries had a minimum wage above 200 U.S. dollars on the continent. With rising inflation, the cost of a tub of Vaseline is higher than quoted and is still rising. More data including more SSA countries will be available before the end of 2024.

See summary slides of this survey in ***Annex 3***

Production cost connected to market price for the two selected options (urea-based; glycerol-based) *(estimate made by our industry consultant of the writing group, Unifarco, Italy)*

To calculate a complete production cost connected to market price, we would need:

- **Industrial cost** (formula, packaging, production costs), that we present below:
- **Distribution cost and selling volumes**, that we still not have; the **market price** (ongoing survey as mentioned above)

The cost of the two formulations proposed is basically the same: **2-2,30 euro/kg.**

Table 4. Cost estimates per kilogram with the basic ingredients discussed in the application

Raw material	Cost
Self-emulsifying system (1° hypothesis)	1,15 euro/kg
Glycerin	0,11 euro/kg
Urea	0,09 euro/kg
Shea butter	0,38 euro/kg
Preservative system (1° hypothesis)	0,06 euro/kg
Preservative system (2° hypothesis)	0,25 euro/kg

For two types of packaging: 400 ml Tube or 500 ml Jar the final **industrial cost** could be around **2,80 euro per piece for the 400 ml Tube, and around 3,50 euro per piece for the 500 ml Jar.**

Therefore, considering the amount of emollient that the patient should apply every weekly for chronic use, we estimate for industrial costs only:

- For adults: approximately 70-140 grams of emollient/moisturizer per week → **around 25-50 euro per year**
- For children: approximately 50- 100 grams per week → **around 18-36 euro per year**

As an example, for the recommended urea-formulation the cost would be around **5 euro/Kg.**

Section 11: Regulatory status, market availability and pharmacopoeial standards

Regulatory status

The proposed moisturizing creams are authorized as medicinal products in several countries in Europe. Their ATC codes are:

- Urea 5% cream D02AE01
- Glycerol 15% cream D02AC
- Glycerol 20% cream D02AX

The Pharmacopeial standards of the active ingredients are:

- Urea (Carbamide): Ph. Eur., USP, BP, CAS Number: 57-13-6;
- Glycerol: Ph. Eur., USP, BP, JP, CAS Number: 56-81-5;

Medicinal products for the treatment of AD can be identified in the medical databases via their ATC codes, e.g. in the EU, UK and USA. However, not only authorized medicinal products are used to treat AD but also those regulated as medical device and cosmetic products are identified on the market. This is due to the responsibilities of the individual EU Member States regarding the budgets for health care, as well as their decisions regarding pricing and reimbursement. A brief description of the regulatory matters relating to the use of the dermatologicals, and their cost implications are described below.

Presenting a product for treatment or prevention of a disease defines the product as a medicinal product *(144)* or a medical device *(145)* in the EU, whereas cosmetics are not allowed to be presented for treatment of skin diseases *(146, 147)*. The EU borderline manual for cosmetics states that moisturizers presented as having "*properties to treat or prevent atopy/atopic skin cannot be qualified as cosmetic products"(148)*. However, patients with diseases, such as those suffering from e.g., AD as well as other diseases, regularly use cosmetics on their skin, such as e.g. soaps, make-up, sunscreens, and moisturizing creams. Therefore, cosmetic creams marketed to be "*appropriate for/suitable to skins with atopic tendency/atopic skin"(149)* are compliant with the regulations. An evidence-based approach is always recommended for selecting moisturizers, as not all cream formulations are the same. Therefore, recommending moisturizers without having evidence on their suitability for treatment of atopic skin should be made with caution.

Another complexity is that the budgets for health care in the EU, as well as decisions regarding pricing and reimbursement, are the responsibilities of the individual Member States. Therefore, different types of reimbursement systems are used to control expenditures and the trade-offs between these conflicting goals *(150)*. Consequently, the resources required to place and retain topical products on the market differ considerably between the regulatory categories, which also are reflected in their costs. In the EU, prescription (Rx) based products are usually reimbursed, but urea-containing and glycerol-based moisturizers are often sold over the counter (OTC) without reimbursement. Notably, not only medicinal products but also cosmetic products containing urea are reimbursed in some countries due to their potential lower price levels. The actual costs for the patients may therefore differ due to different system for reimbursement in the EU.

For example, in Finland the reimbursement system consists of three reimbursement categories where both medicinals and "basic topical ointments" (cosmetics) can be reimbursed. However, an annual maximum is set to limit the amount of co-payments a patient is expected to pay for his/her reimbursable preparations.*(150)* In Sweden, cosmetics are not reimbursed, but only authorized medicinals with for example urea, where also several generic versions to the original preparations are reimbursed. These urea-creams belong to the pharmacotherapeutic group protectives and emollients with ATC code: D02AE01.

Market availability of the proposed medicine(s)

See **annex 3** with the available commercial brands and comments on affordability in 12 countries of SSA

Glycerol 15% cream (Dexeryl) is commercialized with a drug status in the following countries (email communication Voisard JJ, Pierre-Fabre, 2024-06-26, jean.jacques.voisard@pierre-fabre.com)

BENIN	MARTINIQUE
BURKINA FASO	MAURITIUS
CAMEROON	MAURITANIA
CONGO (BRAZZAVILLE)	MAYOTTE
IVORY COAST	MONACO
FRANCE	NIGER
GABON	New Caledonia
GUADELOUPE	French Polynesia
The republic of GUINEA	the Democratic Republic of the Congo
French Guiana	RÉUNION
KAZAKHSTAN	SAINT-MARTIN
KUWAIT	Senegal
LIBYA	Switzerland
MADAGASCAR	TOGO
MALI	TUNISIA
MOROCCO	WALLIS AND FUTUNA

Barriers to availability as discussed earlier in this application concern mostly affordability due to taxes on imported products.

Reference to existing or planned inclusion of the proposed medicine(s) on the WHO List of Prequalified Finished Pharmaceutical Products, should be included, where appropriate.

NA *(151)*

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ANNEX 1 Excerpts from the systematic reviews and general summary of the analysis for all moisturizers (data for urea and glycerol detailed in the application)

In the following, results from the systematic reviews are presented in reverse order of publication with particular emphasis on the medicines and drug substances identified by the authorities with an ATC-code and those identified from promising outcomes in the clinical studies. The texts are excerpted *in extenso* from the publications.

The publications referred to in the individual reviews are found in the actual review and are crossed out in the excerpts for clarity.

- **Results from the systematic reviews years 2008-2023**

Sidbury 2023 *(4)*

The most recent systematic review contained guidelines of care for the management of atopic dermatitis in adults with topical therapies, published by the American Academy of Dermatology (AAD), also including, for example, corticosteroids ***(4)***. For adults with AD, the AAD strongly recommended the use of moisturizers, but could not recommend a particular moisturizer or active ingredient in an emollient based on the limited available evidence.*(4)*

The authors conclude that moisturizers were shown to reduce signs, symptoms, and inflammation in AD, to improve AD severity and to increase time between AD flares. They noted that topical moisturizers target xerosis by minimizing transepidermal water loss and improving stratum corneum hydration and are integral to nearly all AD management plans, as they are typically utilized as part of a comprehensive regimen with pharmacologic treatments, but may also be used as monotherapy in mild cases.

“An analysis of 5 moisturizer studies (including 500 patients) showed a small reduction in AD severity with the use of moisturizers as measured by the SCORing Atopic Dermatitis (SCORAD) tool and the Eczema Area and Severity Index (EASI) (standardized mean difference [SMD] of 0.51, 95% confidence interval [CI]: 0.17-0.85.” Supplementary data from the publication are given below (available via Mendeley at https://data.mendeley.com/datasets/fmkr7fwx9j/2).

“Of note, SMD indicates the size of the intervention effect relative to the variability observed in a study; an SMD of 0.2 to 0.5 is considered to represent a small effect, while an SMD of 0.5 to 0.8 represents a moderate effect.71 Results varied, however, while one study reported a small but significant improvement in AD severity (mean EASI score decreased from 28.3 to 24.3, P = .024) with use of a moisturizer containing hyaluronic acid, telmesteine, *Vitis vinifera*, and glycyrrhetinic acid,8 another study did not find an improvement in SCORAD between a glycerol-based emollient and placebo in 24 patients.9 Analysis of 3 studies demonstrated patient assessment of disease severity improved in the experimental groups (79% vs 42.9%), though it did not reach significance (Risk ratio [RR]: 2.24, 95% CI: 0.89-5.64).6,8,10

Moisturizers may also help reduce itch. A study comparing a moisturizing cream containing lipopolysaccharide derived from *Pantoea agglomerans* to a vehicle found a significant difference in itch improvement (assessed via visual analog scale [VAS] scores) at week 4

(P\.01).13 Itch improvement was demonstrated in other studies,8 though a study comparing an ectoine-containing cream to a nonsteroidal anti-inflammatory cream did not note a significant difference between treatment groups.11 Various types of moisturizers, including emollients, occlusive agents, and humectants are commercially available, each with its own mechanism leading to improved skin hydration. Studies examining moisturizer use in AD vary by type of moisturizer, study design, and outcomes assessed. Thus, the use of any particular moisturizer or active ingredient in an emollient cannot be recommended based on the limited available evidence.

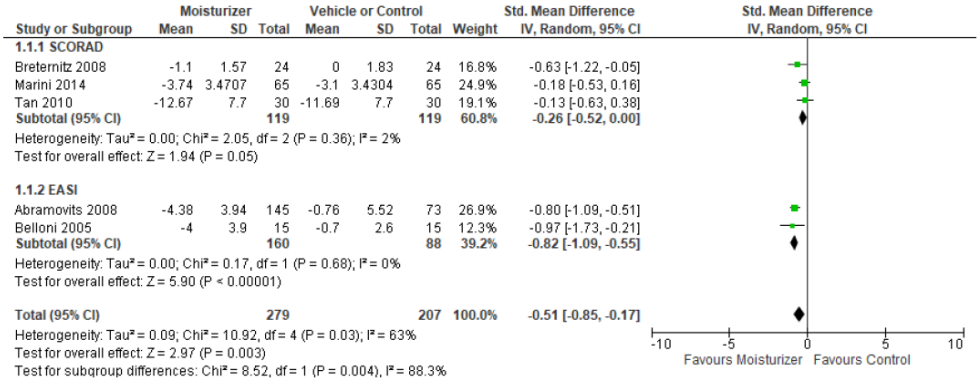
The literature on AD treatment supports a strong recommendation for moisturizer use based on moderate certainty evidence (Table III). Moreover, moisturizers are generally safe, with rare serious adverse effects. Examination of 5 studies found adverse events (ie, mild and cutaneous) occurring in 34.3% of patients in the treatment arms versus 22.1% of patients in the control arms (RR: 1.32, 95% CI: 1.01-1.74),6,8,10,14,15 though withdrawal due to adverse events is uncommon.6,8 Important considerations in moisturizer use include allergenic potential (many vehicles and interventions contained known contact allergens and innumerable ingredients), palatability, heterogeneity in formulations and trial data, paucity of data in AD patients with skin of color, and cost.

Two points warrant further mention: (1) while moisturizing is generally superior to lack of moisturizing, the vehicle in emollient studies is often as effective as the vehicle plus active ingredient, and (2) studies of emollients usually do not examine the use of moisturizers on actively dermatitic/inflamed skin.”

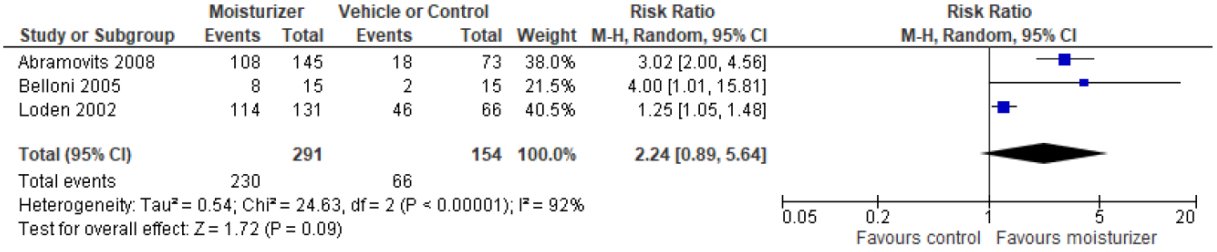
In summary, AAD made **strong recommendations** for the use of **moisturizers,** topical corticosteroids (TCS), calcineurin inhibitors (TCI), Janus kinase (JAK) inhibitors, phosphodiesterase-4 inhibitors (PDE-4) were made, whereas **conditional recommendations** were made for the use of bathing and wet wrap therapy and the AAD **were against the use** of topical antimicrobials, antiseptics, and antihistamines *(4)*.

Table. Supplementary data from the guidelines for care of AD from the American Academy of Dermatology (AAD) are shown below (available via Mendeley at https://data.mendeley.com/datasets/fmkr7fwx9j/2). Definitions, abbreviations and references are found in the article.

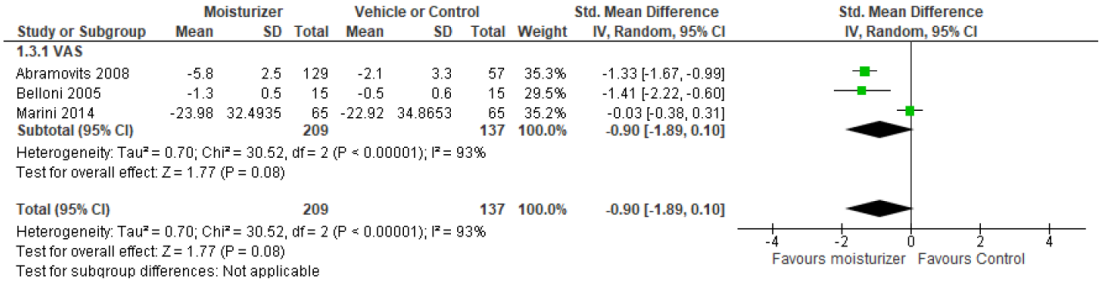
Analysis 1a. Change in disease severity as assessed by investigators (SCORAD & EASI)



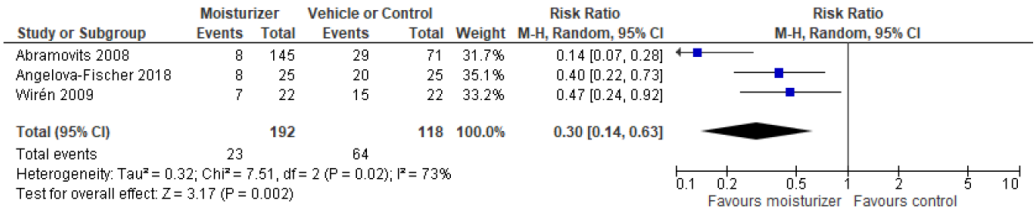
Analysis 1b. Number of participants who experienced improvement (self-assessed)



Analysis 1c. Change from baseline in itch.



Analysis 1d. Number of participants who experienced a flare.



Nugroho et al 2023*(93)*

This study aimed to compare the efficacy of moisturizers containing ceramide with other moisturizers for AD management, using a systematic evaluation procedure. Five articles met the eligibility and inclusion criteria.

A meta-analysis of TEWL results in three articles found that **TEWL values were not significantly different in subjects treated with ceramide-containing moisturisers** (mean difference: −3.56, 95% CI [−8.63,1.52], *P* = 0.17) with high heterogeneity (I 2= 92%) compared to other treatments.

The change in **SCORAD (two articles) was significantly higher in moisturizers containing ceramide** (mean difference: −0.98, 95% CI [−1.63, −0.33], P = 0.003) with low heterogeneity (I = 0%).

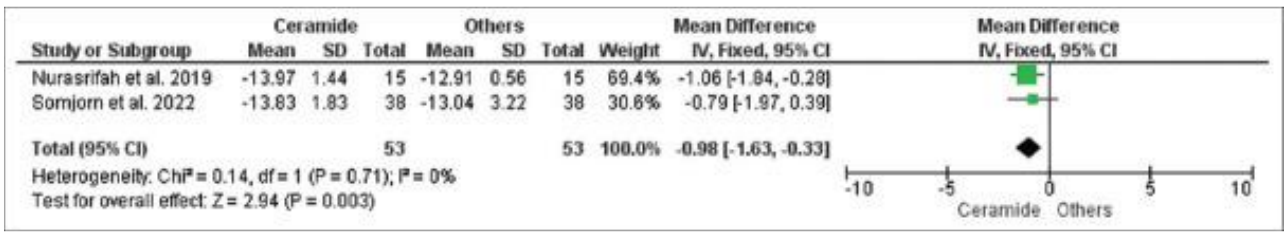
Moisturizers containing ceramide improve SCORAD and TEWL; however, only the changes in SCORAD in moisturizers containing ceramide is superior to other moisturizers.

Table 2

Data extraction table

Authors	Country	Study Type	Total Sample	Intervention	Comparison	Follow-Up Time	Outcome
Mustifah *et al.*,[17] 2018	Indonesia	Double-blind, RCT	15	Cream B (ceramide)	Cream A (*Aloe vera*)	Second week	TEWL
Tabri and Yuniati,[15] 2018	Indonesia	Double-blind, RCT	16 (ceramide 1%: 4, lanolin 10%: 4, urea 10%: 4, control: 4)	Ceramide 1%	Lanolin 10%	Day 14	TEWL
Somjorn *et al.*,[11] 2022	Thailand	Double-blind, RCT	38	Linoleic acid, 5% dexpanthenol and ceramide (LDC cream)	Urea 5% cream	Second and fourth week	SCORAD
Fischer *et al.*,[16] 2018	Germany	Double-blind, RCT	26	Placebo (replaced by water)	Glycerol (10%), evening primrose (6%) and grapeseed oil (6%), rich in omega-6 fatty acids, ceramide 3 and licochalcone A (<1%)	Baseline, first, second, fourth, eighth, and twelfth week	TEWL
Nurasrifah *et al.*,[12] 2019	Indonesia	Double-blind, RCT	30	Petrolatum	Ceramide, polidocanol, and menthol	Baseline, first, second, and fourth week	SCORAD

Forest plot for SCORAD



SCORAD changes data

Article	Year	Intervention	SCORAD		
			Mean	SD	*N*
Nurasrifah *et al.*[12]	2019	Ceramide	−13.97	1.44	15
		Petrolatum jelly	−12.91	0.56	15
Somjorn *et al.*[11]	2022	Ceramide	−13.83	1.83	38
		Urea	−13.04	3.22	38

TEWL data

Article	Year	Intervention	TEWL		
			Mean	SD	*N*
Mustifah *et al.*[17]	2018	Ceramide	6.55	3.25	15
		Aloe vera	7.39	3.17	15
Fischer *et al.*[16]	2018	Ceramide	11.32	1.47	26
		Placebo	18.36	1.75	26
Tabri and Yuniati[15]	2018	Ceramide	11.62	3.58	4
		Lanolin	13.62	5.68	4

Fishbein et al. 2019*(95)*

The study aimed to determine the safety and efficacy of topical corticosteroid versus vehicle/moisturizer in children under 2 years old (<2 y) using results from RCT. However, as only one study limited analyses to children <2 y, the review included participants older than 2 years, and therefore a short summary is given in the present overview. Twelve RCTs were included with 2224 participants.

“The study concluded that topical corticosteroids trended to being more effective and equally safe to vehicle/moisturizers, but generalizability is limited given the dearth of well-designed studies focused on children <2 y.

Only 2 studies compared topical corticosteroid to a true moisturizer, while the rest used vehicle. Interestingly, many vehicle studies showed a high proportion of responders. Our findings are consistent with the NHS-sponsored systematic review of RCTs comparing topical corticosteroids versus placebo to treat AD across age groups, which reported a large treatment effect of topical corticosteroids, “without evidence of harm” (Hoare, Li Wan Po, & Williams, 2000; Nankervis et al., 2016).

With regards to adverse events, we found that the **vehicle/moisturizer group had a slightly higher, but not significant, rate of adverse events versus the topical corticosteroid group** (0.17 versus 0.12). Lower potency topical corticosteroids also showed a slightly higher rate of adverse events as compared to higher potency corticosteroids. This could be partly explained by the bias of the studies included in our review. Eight of the studies were funded

by topical corticosteroid companies, and in industry funded moisturizer studies, lower potency corticosteroids were used as the comparator. However, inadequate treatment of AD appears to result in **significant skin infections and side effects more often than topical corticosteroids**.

Local skin irritation was the most common side effect from both moisturizer and topical corticosteroids. Similar to previously published studies, less than 0.2% of subjects developed cutaneous side effects linked to topical corticosteroids (skin atrophy, striae, acne, telangiectasia)."

A summary table of the results is given below.

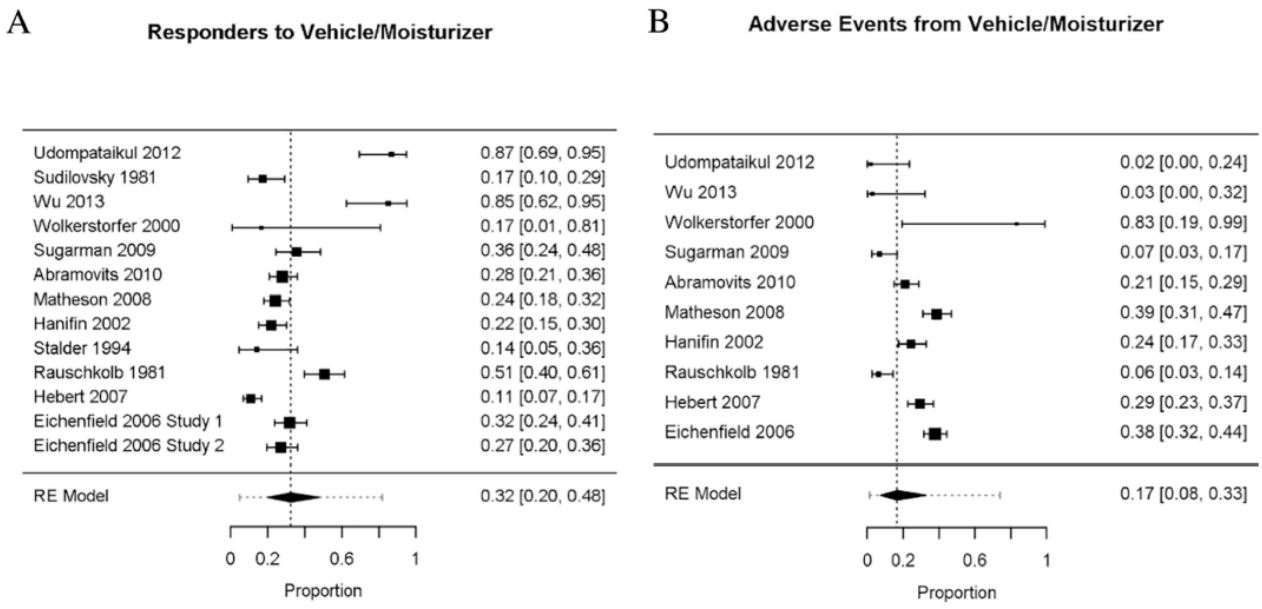


Figure 3.
Forest plot of proportions by study (solid square is the mean proportion), number on the right. 95% confidence interval (CI) represented by bars on graph, summarized in brackets on the right. Larger squares represent more participants in the study. RE (Random-Effects Model) summarizes data from all studies, with the dashed vertical line displaying the overall proportion of responders/events from the aggregate data, and the horizontal dashed line representing the 95% CI across studies.

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Tasker et al. 2020 ***(94)***

This review is part of a series of annual updates that summarize the evidence base for atopic eczema (AE). The aim is to provide a succinct guide for clinicians on the key findings from 14 systematic reviews on the prevention and topical treatment of AE published or indexed in 2018. The review focused mainly on oral treatment during pregnancy and in newborns. The following learning points were given on topical treatment:

- There is weak evidence of a low risk of reversible hypothalamic-pituitary-adrenal axis suppression following 2-4 weeks of treatment with low-potency topical steroids.
- There is conflicting evidence as to whether bleach bath, compared with water batch, have any effect on skin flora and AE severity.
- A single study demonstrated that the topical Janus kinase inhibitor tofacitinib at 2% significantly reduces the Eczema Area and Severity Index compared with vehicle.
- Topical naltrexone cream 1% improves pruritus (measured using a visual analogue scale) by 30% more than placebo.
- There is weak evidence that topical alternative therapies, including antioxidants, micronutrients and some herbal medicines (*M. aquifolium*), may improve AE.

Van Zuuren et al. 2017 ***(3, 96)***

In an extensive Cochrane review from 2017, performance and quality of as many as 77 randomized controlled trials in people with eczema were evaluated (6603 participants, mean age: 18.6 years; mean duration: 6.7 weeks) in 2017.*(3, 96)* Seven studies (9%) were reported to be at low risk of bias, 34 (44%) had unclear risk and 36 (47%) were at high risk. The quality of the evidence was mainly low or moderate for the prespecified outcomes.

The Cochrane analysis concluded that the most important comparison, **'moisturizer vs. no moisturizer', showed improved Scoring Atopic Dermatitis values in the moisturizer group** compared with no moisturizer [mean difference -2·42, 95% confidence interval (CI) -4·55 to -0·28], but did not meet the minimal important difference of 8·7.

Moisturisers led to lower investigator-assessed disease severity (12 studies, 1281 participants, SMD -1.04, 95% CI -1.57 to -0.51; high-quality evidence) and fewer flares (six studies, 607 participants, RR 0.33, 95% CI 0.17 to 0.62; moderate-quality evidence), but there was no difference in adverse events (10 studies, 1275 participants, RR 1.03, 95% CI 0.82 to 1.30; moderate-quality evidence).

Topical active treatment combined with moisturiser was more effective than active treatment alone in reducing investigator-assessed disease severity (three studies, 192 participants, SMD -0.87, 95% CI -1.17 to -0.57; moderate-quality evidence) and flares (one study, 105 participants, RR 0.43, 95% CI 0.20 to 0.93), and was preferred by participants (both low-quality evidence).

Participants considered moisturisers more effective in reducing eczema (five studies, 572 participants, RR 2.46, 95% CI 1.16 to 5.23; low-quality evidence) and itch (seven studies, 749 participants, SMD -1.10, 95% CI -1.83 to -0.38) than control. Participants in both

treatment arms reported comparable satisfaction (three studies, 296 participants, RR 1.35, 95% CI 0.77 to 2.26; low-quality evidence).

There were **fewer flares with moisturisers** (two studies, 87 participants, RR 0.40, 95% CI 0.23 to 0.70), time to flare was prolonged (median: 180 versus 30 days), and less topical corticosteroids were needed (two studies, 222 participants, MD -9.30 g, 95% CI -15.3 to -3.27). The rate of flares was reduced (hazard ratio 3·74, 95% CI 1·86-7·50). Adding moisturizers to topical anti-inflammatory treatment was more effective than anti-inflammatory treatment alone and resulted in fewer flares. For example, more flares were reported with moisturizer alone than when combined with twice-weekly fluticasone propionate (risk ratio 2·17, 95% CI 1·55-3·11).

In the Cochrane review, urea-, glycerol-, and glycyrrhetinic acid-containing creams were reported to work better than their controls (vehicle, placebo or no moisturizer) according to both participants and physicians, whereas the evidence for **oat** and other proposed preparations were less certain:

- There is **low to moderate quality** evidence that **urea**-containing creams are more effective than no moisturiser, placebo or vehicle (based on both investigator and participant assessments), and **reduced rate of flare by a third**, but with more adverse events. Efficacy was confirmed by one study, at low risk of bias, conducted over 180 days, that showed that **barrier-strengthening moisturiser with 5% urea reduced the number of participants who experienced a flare, and increased time to flare** in comparison to the reference cream.
- There is **moderate to high quality** evidence that **glycerol**-containing moisturisers are more effective than 'vehicle' or placebo (investigator and participant assessments), but the MID was not met.
- There is **moderate quality** evidence that Atopiclair (**glycyrrhetinic acid**) is more effective than vehicle (investigator and participant assessments), but the MID was not met. It also had an important **effect on itch and on reduction of flares**.
- There is **low to very low-quality** evidence that there is no difference in efficacy between **oat**-containing cream and vehicle or no moisturiser (investigator and participant assessments), and more adverse events were seen.

Therefore, the results from some of these substances are excerpted from the Cochrane review and presented in the following:

<u>Urea</u>

Four studies evaluated urea-containing cream. Participants reported skin improvement more frequently with urea-containing cream than placebo (one study, 129 participants, RR 1.28, 95% CI 1.06 to 1.53; low-quality evidence), with equal satisfaction between the two groups (one study, 38 participants, low-quality evidence).

Urea-containing cream improved dryness (investigator-assessed) more frequently (one study, 128 participants, RR 1.40, 95% CI 1.14 to 1.71; moderate-quality evidence) with fewer flares (one study, 44 participants, RR 0.47, 95% CI 0.24 to 0.92; low-quality evidence), but more participants in this group reported adverse events (one study, 129 participants, RR 1.65, 95% CI 1.16 to 2.34; moderate-quality evidence).

It is worth mentioning the low risk of bias Åkerström 2015 study *(43)*, which compared a barrier-strengthening moisturiser containing 5% urea against a reference cream without urea.

This study started with a stabilisation phase in which active treatment (mometasone) was used until the eczema was (almost) cleared. During the maintenance phase of 180 days without active treatment, fewer participants in the group using barrier-strengthening moisturiser with 5% urea experienced a flare compared to those using the reference cream, and **the time to flare was considerably lengthened (15 compared to 22 days**).

Glycerol

Three studies assessed glycerol-containing moisturiser versus vehicle or placebo. **More participants in the glycerol group noticed skin improvement** (one study, 134 participants, RR 1.22, 95% CI 1.01 to 1.48; moderate-quality evidence), and this group saw **improved investigator-assessed SCORAD** (one study, 249 participants, MD -2.20, 95% CI -3.44 to -0.96; high-quality evidence), but MID was unmet. Participant satisfaction was not addressed. The number of participants reporting adverse events was not statistically significant (two studies, 385 participants, RR 0.90, 95% CI 0.68 to 1.19; moderate-quality evidence).

Glycyrrhetinic acid (ingredient in Atopiclair)

Three studies on **Atopiclair,** 174/232 participants experienced **improvement in participant-assessed disease severity** versus 27/158 allocated to vehicle (RR 4.51, 95% CI 2.19 to 9.29). Atopiclair **decreased itching** (four studies, 396 participants, MD -2.65, 95% CI -4.21 to -1.09) and achieved more frequent satisfaction (two studies, 248 participants, RR 2.14, 95% CI 1.58 to 2.89), fewer flares (three studies, 397 participants, RR 0.18, 95% CI 0.11 to 0.31), and lower EASI (four studies, 426 participants, MD -4.0, 95% CI -5.42 to -2.57), but MID (6.6) was unmet. The number of participants reporting adverse events was not statistically different (four studies, 430 participants, RR 1.03, 95% CI 0.79 to 1.33). Evidence for these outcomes was moderate quality.

Oat

Four studies investigated oat-containing moisturisers versus no treatment or vehicle. **No significant differences between groups were reported for participant-assessed disease severit**y (one study, 50 participants, RR 1.11, 95% CI 0.84 to 1.46; low-quality evidence), satisfaction (one study, 50 participants, RR 1.06, 95% CI 0.74 to 1.52; very low-quality evidence), and investigator-assessed disease severity (three studies, 272 participants, standardised mean difference (SMD) -0.23, 95% CI -0.66 to 0.21; low-quality evidence). In the oat group, **there were fewer flares** (one study, 43 participants, RR 0.31, 95% CI 0.12 to 0.7; low-quality evidence) and **less topical corticosteroids** needed (two studies, 222 participants, MD -9.30g, 95% CI 15.3 to -3.27; low-quality evidence), but more adverse events were reported (one study, 173 participants; Peto odds ratio (OR) 7.26, 95% CI 1.76 to 29.92; low-quality evidence).

Adverse events

None of the studies reported aspects such as the smell or stickiness or greasiness of the moisturiser, but rather pruritus, stinging, smarting or increase in erythema and folliculitis.

Nankervis et al 2016 ***(5)***

This is a book chapter which summarises new RCT evidence on topical eczema treatments that do not fit into other categories, according to the authors. Studies on urea, glycerine and ceramides are excerpted below.

Other topical treatments [*Hippophae rhamnoides*, black seed oil, pill mask, rosmarinic acid, *Vitreoscilla filiformis*, shale oil, miltefosine, opiate receptor antagonist, carbohydrate-derived fulvic acid, raffinose, farnesol and xylitol, bacterial antigens, chamomille extract, heparin and levomenol, 15(R/S)-methyl-lipoxin A, *N*-acetyl-L-hydroxyproline, nalmefene hydrochloride monohydrate (SRD174)] were tested in one trial reported from 2000 onwards. None of the trials found any evidence of benefit for the treatment tested compared with placebo or, in the case of licochalcone A, compared with hydrocortisone.

The following products were also presented, but are not discussed further in the present summary:

- Albolene (DSE Healthcare Solutions) was compared with a prescription device emollient MimyX, (Stiefel Laboratories) with concurrent use of topical triamcinolone (0.1%) cream
- Exomega milk (Pierre Fabre Limited)
- Sunflower oleodistillate (2%)-containing emollient (Stelatopia; Mustela DermoPediatrie, Laboratoires Expanscience)
- Hyaluronic acid-based foam emollient (Hyaltopic; Onset Therapeutics) against a ceramide-based emollient (EpiCeram).
- Bath additives
- Furfuryl palmitate (the vehicle was superior)
- Vitamin B12
- WBI-1001
- Protease inhibitor SRD441
- Atopiclair (Graceway Pharmaceuticals)
- Camellia oil
- Cipafylline cream
- Lipoxin A4

Urea and glycerol emollients

"Two virtually identical trials by Loden and colleagues,[193,194] each lasting for 30 days, compared a glycerine cream (20%) with its vehicle (with glycerine substituted with water) and a cream containing urea (4%) and sodium chloride (4%). For the earlier trial[193] the treatment was applied only twice a day to a patch of dry skin identified by the dermatologist. For the second trial[194] participants were allowed to use the treatments as much as necessary and at least once a day. The first trial was primarily concerned with physical markers of efficacy but also measured skin dryness. The second trial was more concerned with efficacy and measured both participant- and investigator-assessed skin dryness, as well as participant-assessed degree of stinging, smarting, itching and dryness/irritation.

A trial by Bissonnette and colleagues[195] compared a urea moisturiser (5%) against a urea lotion (10%) but did not include a control arm. The trial included 100 adults aged > 18 years with mild eczema (SCORAD score of < 30) and treatments were applied twice daily for 42 days.

A trial by Amichai and Grunwald[196] compared the liquid soap Axera™ (Perrigo-Pharma), containing 12% ammonium lactate and 20% urea, with a commercially available liquid soap for showering over a 3-week period. No other emollients or soaps were permitted during the trial but participants could continue to use their current eczema treatments. The study included 36 adults and children aged 3–40 years with mild to moderate eczema, diagnosed according to the UK Working Party's criteria.[9]

Assessment of risk of bias

Urea and glycerine emollients: risk of bias of the included studies

Benefits

The trial report by Loden and colleagues[193] gives very little detail and the two graphs that present the data on dryness score appear to show very different baseline scores for the three treatment groups, with the urea group having a noticeably higher baseline score than the glycerine and placebo groups. No details are given about the method of randomisation or whether allocation concealment took place and the difference in baseline values raises doubts about these procedures. Although no detailed data are presented, the trial report states that after 30 days' treatment the urea treatment group had a significantly lower dryness score than the glycerine treatment group ($p = 0.021$). It is unclear whether this refers to the difference between the final dryness scores or the difference between the change in dryness scores.

The second trial by Loden and colleagues[194] used a dermatologist-assessed dryness scale, with no statistically significant differences reported between urea cream and glycerine cream and between glycerine cream and placebo cream. For participant assessment of dryness at the end of treatment there was no significant difference between the urea and glycerine groups (89% vs. 85% of participants rating the dryness as 'improved'; $p = 0.77$). The proportion of participants rating the dryness as 'improved' was significantly higher in the glycerine cream group than in the placebo group (89% vs. 69%; $p = 0.019$). Again, no detailed data are presented, including any baseline scores or demographics.

The trial by Bissonnette and colleagues[195] did not find a statistically significant difference in eczema severity between the urea cream (5%) and the urea lotion (10%) after 42 days of treatment (19.76% vs. 19.23% reduction in mean SCORAD scores). The trial report states that the urea cream (5%) had better cosmetic acceptability than the urea lotion (10%).

Amichai and Grunwald[196] reported significant reductions for the urea and ammonium liquid soap (Axera) compared with the commercially available liquid soap in scaling (urea and ammonium soap: from 1.63 to 0.68, 'placebo' soap: from 1.75 to 1.42; $p < 0.0001$), skin dryness scaling (urea and ammonium soap: from 1.88 to 0.77, 'placebo' soap: from 1.83 to 1.25; $p < 0.0001$), redness (urea and ammonium soap: from 0.58 to 0.14, 'placebo' soap: from 0.62 to 0.53; $p = 0.03$) and participant-assessed itching (urea and ammonium soap: from 1.38 to 0.32, 'placebo' soap: from 1.83 to 0.92; $p < 0.001$). The participants rated the urea and ammonium soap significantly better for its non-sticky texture and for the improvement of skin smoothness; however, no data were provided for this outcome.

Harms

Information about adverse events was not recorded in the first trial by Loden and colleagues.[193]

Adverse events that could possibly be related to study treatment were recorded and graded in the second trial by Loden and colleagues.[194] The report states that adverse skin reactions were significantly lower in the glycerine group than in the urea group, with 10% in the glycerine group experiencing moderate to severe stinging compared with 24% in the urea group ($p < 0.0006$).

In the trial by Bissonnette and colleagues,[195] 22 out of the 100 participants experienced at least one adverse event. Five adverse events were reported as being possibly related to

study treatment and no participant experienced more than two adverse events. Three participants withdrew from the study because of adverse events, two in the urea lotion group because of irritant contact dermatitis and pruritus and one in the urea moisturiser group because of erythema.

In the trial by Amichai and Grunwald[196] one participant in the Axera group had a mild transient skin irritation related to using the soap.

Lipid emollient

One trial by Wiren and colleagues[197] conducted in Sweden compared an emollient with 20% lipid content (Canoderm® cream, ACO Hud) with no treatment until relapse or 6 months. All 55 adults with eczema who were recruited into the trial initially used the topical corticosteroid betamethasone (0.01%) for 3 weeks to induce remission. Only those participants who had 'cleared eczema' according to an assessment by a dermatologist ($n = 44$) were then randomised to the maintenance period of emollient or no treatment. The aim of the trial was to assess whether emollient use prolonged the time spent in remission from eczema.

Assessment of risk of bias

Lipid emollient: risk of bias of the included study

Benefits

The median time to first relapse was > 6 months for the emollient group compared with 30 days when using no treatment. This **difference in time to relapse was statistically significant, with a relative risk reduction of 53% and number needed to treat of 2.8.**

Harms

No information about adverse events was reported.

Emollients containing ceramide.

An industry-sponsored multicentre trial by Sugarman and Parish[126] compared twice-daily application of a ceramide-dominant barrier repair formulation (EpiCeram) against the topical corticosteroid fluticasone propionate (0.05%) (Cutivate™; GlaxoSmithKline) on affected areas in body folds. The trial included 121 infants and children aged from 6 months to 18 years. All of the participants used the emollient lotion Cetaphil™ (Galderma Laboratories) on unaffected areas of skin.

A trial by Berardesca and colleagues[200] compared a lipid mixture containing ceramide-3, cholesterol, palmitic acid and oleic acid in water-in-oil with nanoparticles with the same lipid mixture in combination with topical corticosteroids. Out of a trial population of 508 participants, 91 participants had eczema. All participants applied the treatment once or twice a day until healing had occurred or for a maximum of 8 weeks.

A trial by Draelos[201] compared a ceramide-based emollient against a hyaluronic acid-based foam, the details of which are discussed later in this chapter.

A within-person trial by Simpson and Dutronc[202] compared a body wash and moisturiser containing ceramide (Restoraderm®; Galderma (UK) Ltd) in addition to standard eczema treatment with standard eczema treatment alone. The trial included 127 adults and children aged > 3 years with mild to moderate eczema according to IGA, randomised to emollient treatment twice daily on one side of the body and no emollient treatment on the other side, for an unreported length of time.

Assessment of risk of bias

Emollients containing ceramide: risk of bias of the included studies

Benefits

The industry-funded trial by Sugarman and colleagues[126] did not make it clear whether this was a superiority or an equivalence trial, although the stated aim of the trial seems to have been to prove equivalence. Similar improvements in eczema severity (measured by SCORAD score), pruritus and sleep loss were observed in both groups. The relative reductions in eczema severity, measured using SCORAD score, were fairly large, with the emollient group decreasing from 37.2 to 18.5 and the fluticasone propionate group decreasing from 34 to 12 (estimated from a graph). The reductions in pruritus were also fairly large, with the emollient group decreasing from 6.1 to 2.8 and the fluticasone propionate group decreasing from 5.6 to 2.1 (estimated from a graph). The sleep loss assessments showed a decrease from 4.1 to 1.4 in the emollient group and from 4.1 to 0.7 in the fluticasone propionate group.

The trial by Berardesca and colleagues[200] reported a statistically significant difference in favour of combined treatment with emollient and topical corticosteroids compared with emollient alone for pruritus after 8 weeks ($p = 0.018$), overall disease severity after 4 weeks ($p = 0.007$), dryness and scaling, but no detailed data are provided.

The trial by Simpson and Dutronc[202] found a significant reduction in eczema severity for the ceramide-containing emollient compared with no emollient after 7 ($p = 0.0003$) and 15 ($p = 0.0043$) days while using standard eczema treatment. This difference was not significant at days 21 and 28. There were no absolute values reported. The mean change was not explicitly stated but appears to have been no more than –1.0 in the no treatment group and –1.4 in the ceramide-containing emollient group, as determined from a graph.

Harms

Berardesca and colleagues[200] did not report any information on adverse events. In the trial by Sugarman and colleagues[126] there were no serious adverse events and four participants in the emollient group had a worsening of eczema that required rescue medication. Simpson and Dutronc[202] did not report information about adverse events.

Overall implications for research and practice

Three of the five trials show a significant **improvement in IGA** for participants treated with Atopiclair compared with those treated with vehicle, with two also reporting **an improvement in EASI** score.[225–227] No conclusions can be drawn from the trial by Belloni and colleagues[224] as no between-treatment comparison was performed. One trial showed no difference between Atopiclair and two other emollients for IGA and EASI.[199]

Overall, there is **reasonable evidence of benefit for Atopiclair** compared with vehicle. Further trials comparing Atopiclair against other active treatments are required and these should ideally be independent from the manufacturers of any interventions involved.”

Lindh and Bradley 2015

The effectiveness of moisturizers in the treatment of AD and related conditions, such as hand dermatitis, and/or ichthyosis vulgaris, was evaluated by means of a systematic review. The authors concluded that out of the 595 publications initially identified, 45 (48 studies, 3262

patients) were eligible for inclusion. Excerpts from the review are given below, where the majority of references can be found in the original report.

A vast majority of studies indicate that moisturizers have beneficial effects on clinical symptoms [SCORAD (SCORing Atopic Dermatitis) reductions ranging from 0 to 2.7 points], TEWL (range 0 to -12.2 g/m(2)h) and stratum corneum hydration (range +8 to +100%). Direct comparisons between individual moisturizers are still scarce, but the clinical effect appears to be **much more well-documented for urea and glycerin than, for example, propylene glycol, lactate, ceramide, and aluminum chlorohydrate. Compared with urea studies, glycerin studies were more often associated with a high risk of bias**.

Urea

Three of the ten studies compared urea versus no emollient in patients with hand eczema [17], AD [19], or ichthyosis vulgaris [23]. The former two studies used urea in a concentration of 5 % and showed significant beneficial effects on time to relapse during a follow-up of 6 months. The third study used a higher urea concentration of 10 %, and, although an apparent improvement compared with controls was observed, the effect was not statistically tested.

Four studies compared urea versus plain emollients (water-oil emulsions without urea or other ‘active’ substances): three in adults with AD [28, 29, 32] and one in patients with ichthyosis vulgaris [30]. In 172 patients whose AD lesions had been cleared by means of corticosteroids, 6 months of treatment with urea 5 % significantly prolonged the time to relapse (HR 0.63, p = 0.011) [32]. In the other two AD studies, urea 4 % was merely used as a positive control, and no formal comparison was made between urea and plain emollient [28, 29]. However, in the larger of the two studies, urea was superior to glycerin with regard to skin dryness (p = 0.024), the study’s principal clinical outcome. Since the effect of glycerin was very similar to that of the plain emollient, this provides an indirect indication that urea may have an advantage over plain emollients [28]. In the other study, the effect of urea on dryness and irritation was very similar to that of glycerin, once again providing indirect support of urea’s superiority over a plain emollient. However, compared with glycerin, urea was significantly more prone to cause smarting as an adverse effect [29]. In the ichthyosis vulgaris study, clinicians deemed urea 10 % more effective than a plain emollient (p\0.05), but the authors may not have chosen the optimal statistical method for statistical significance testing [30].

Different concentrations of urea have been compared back-to-back in two studies, both including patients with AD [27, 31]. In the first study, urea in concentrations of 5 and 10 % had very similar effects on SCORAD (-19.76 and -19.23 %, respectively, p = 0.37) [27]. However, cosmetic acceptability was rated significantly higher for the 5 % preparation (p = 0.001). This study had a relatively high drop-out rate (16 % during 5 weeks), which could have introduced bias since the analysis was performed per protocol, i.e., disregarding patients who failed to fulfil study participation. In the second study, urea 10 % had a significantly better effect on eczematous eruptions (p = 0.01) and skin dryness (p\0.05) compared with urea 5 % [31]. However, the high- and low-concentration preparations also differed by containing lactic acid and propylene glycol, respectively.

Two studies have compared the clinical effect of urea with that of another active compound, glycerin [26, 28]. In an investigator-blinded, 4-week study, urea 10 % was superior to glycerin against ichthyosis vulgaris symptoms as measured by Specific Symptom Sum Score (SRRC) (p = 0.0001) and global efficacy score (p = 0.0001) [26]. The second study, mentioned above, indicated superiority of urea 4 % over glycerin 20 % in reducing skin dryness in AD [28].

Glycerin

The clinical effectiveness of glycerin-based emollients has been investigated in eight studies, including a total of 2029 subjects [16, 22, 24, 28, 29, 33–35]. In four of these studies, the risk of detection bias was deemed to be high, due to incomplete blinding of outcome assessment [15, 16, 22, 35]. In addition, there was a high risk of selection bias due to incomplete allocation concealment in one study [22] and a high risk of performance bias due to incomplete blinding of participants in one study [15]. Two studies had high drop-out rates that resulted in a high risk of attrition bias [33, 35]. Taken together, a high risk of bias via at least one mechanism was encountered in five of the eight studies. Three of these studies compared glycerin versus no moisturizer: two in children with AD [16, 22] and one in workers with a high risk of developing irritant hand dermatitis [24]. The first of these studies included only 12 children and compared treated with untreated skin areas within each subject. During a follow-up of 2 weeks, the emollient was superior to no treatment in reducing dermatitis symptoms (SCORAD -3.3 vs. -0.6 points, p\0.001). However, the allocation procedure was not described, and whether investigators were blinded to treatment allocation when assessing the outcome was unclear [16]. The second study included 173 children with AD who were randomized to an emollient containing glycerin and Rhealba oat extracts. In addition, participants were allowed to use a corticosteroid (desonide) as needed. During a follow-up of 6 weeks, neither steroid consumption nor improvements in SCORAD or QOL differed between the two study groups [22]. In the irritant dermatitis study, glycerin reduced the 6-month incidence of cutting fluid dermatitis by 51 % compared with no emollient (36 vs. 74 %), but the difference was not subjected to a formal statistical test. However, a three-group test simultaneously comparing glycerin, a barrier cream and no treatment failed to find any significant between-group differences in clinical effect [24]. Four studies have compared glycerin-based emollients versus glycerin-free vehicle [28, 29, 33, 34]. All were double-blind randomized controlled trials with approximately 4 weeks of follow-up. The largest of these studies included 231 children with ichthyosis and showed that glycerin reduced pruritus ($p = 0.01$) and increased the number of responders (60.3 vs. 43.5 %, $p = 0.008$) compared with vehicle alone [33]. In a study in 151 adult patients with AD, glycerin significantly reduced dryness and irritation as evaluated by a dermatologist ($p = 0.0004$) [29]. In contrast, two other AD studies failed to show any significant effects of glycerin on skin dryness, SCORAD, or local severity score [28, 34].

As mentioned above (see Sect. 3.2.2.1), two randomized studies indicate that glycerin is inferior to urea in the symptomatic treatment of ichthyosis vulgaris and AD [26, 28], while a third study in AD patients found no such difference [29]. When comparing glycerin with propylene glycol, a small study in children with AD failed to show any differences in SCORAD reduction after 4 months (p value not significant), but the preparations also differed in other ways (the glycerin emollient contained ice plant extract and natural lipids, while the control emollient was petrolatum based) [35].

Others

In addition to urea, glycerin and propylene glycol, several other moisturizer components have been investigated in clinical trials.

While the clinical effect of urea has been investigated in nine studies (717 patients) and glycerin in seven studies (1831 patients), only two studies (111 patients) have evaluated the clinical effectiveness of propylene glycol. In addition, only one of the latter studies showed any beneficial effects of propylene glycol, as compared with no treatment [21].

For other constituents such as lactate, ceramide, aluminum chlorohydrate, and olive oil [43], the documentation of clinical efficacy is very scarce. In AD patients treated with steroids, addition of a ceramide-containing cleanser and moisturizer increased the chance of disease clearance fivefold, from 15 to 76 % ($p = 0.0001$) and improved the global disease severity significantly ($p = 0.04$) [36]. In contrast, a small 3-week comparison between a ceramide-containing and a ceramide-free emollient failed to show any differences in clinical effect as measured by investigator's global assessment (IGA) and three other scoring systems [37].

In the absence of direct comparisons between emollients, the level of documentation for individual components could potentially guide the choice of a first-line therapy. From this aspect, there are clear differences between available emollients. While the clinical effect of urea has been investigated in nine studies (717 patients) and glycerin in seven studies (1831 patients), only two studies (111 patients) have evaluated the clinical effectiveness of propylene glycol. In addition, only one of the latter studies showed any beneficial effects of propylene glycol, as compared with no treatment [21]. For other constituents such as lactate, ceramide, aluminum chlorohydrate, and olive oil [43], the documentation of clinical efficacy is very scarce. Although a single study indicated favorable effects of olive oil, a more recent study raises concerns that it may actually have deleterious effects on the SC integrity and promote erythema [57]. When comparing the two most well-documented moisturizer components, it is worth noting that a high risk of bias was encountered in five of eight glycerin studies, while this was only true for one of the ten urea studies. This, together with a clinical superiority of urea versus glycerin in two back-to-back comparisons, suggests that urea is well-suited as a first-line moisturizer.

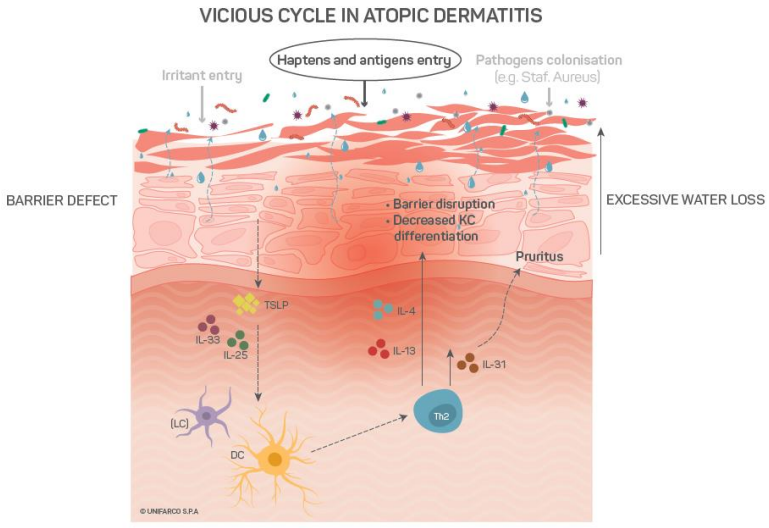
Annex 2: EMOLLIENTS FOR ATOPIC DERMATITIS: FORMULATIVE CONSIDERATIONS

Patients with AD show an alteration of the skin barrier. Due to the altered cutaneous barrier, they are at greater risk of developing contact dermatitis [Simonsen et al., 2018; Bonamonte et al., 2022]. Furthermore, AD patients are repeatedly exposed to topical treatments, which may contain contact allergens with potential sensitizing properties.

Moreover, the relationship between contact allergy and AD seems to be even more complex as different immune pathways (Th1, Th2, and even Th17 mediated ones) may be shared by both entities [Bonamonte et al., 2022].

According to the literature, the frequency of contact sensitization in AD varies from 6.2% to 89% in different countries around the world, with an average of around 40% [Simonsen et al., 2017].

The most frequently reported contact allergens in AD are metals (nickel sulphate, cobalt chloride, and potassium dichromate), lanolin alcohol, neomycin sulphate, formaldehyde, sesquiterpene lactone mix, Compositae mix, and fragrances. A recent multicentric retrospective study, has analysed the prevalence of contact sensitivity in children aged from 0 to 14 years undergoing patch testing for eczematous dermatitis. The most frequent contact allergens were nickel sulphate (10.2%), cobalt chloride (6.7%), methylisothiazolinone (3.7%), fragrance mix-2 (3.2%), potassium dichromate (2.8%), fragrance mix-1 (2.1%) and methylchloroisothiazolinone/methylisothiazolinone (2.1%). [Bonamonte et al., 2022]. Considering that also some “hypoallergenic” personal care products can contain powerful contact allergens, lanolin and fragrances were recently reported as the most common allergens in AD children by European and North American researchers [Lubbes et al., 2017; Warshaw et al., 2009].



For these reasons, an emollient for atopic skin must limit the number of ingredients, avoiding the molecules that most commonly cause sensitization, based on the most recent publications in the dermatological field. On the other hand, all those ingredients that can provide benefit are to be preferred: promoting barrier repair, restoring skin hydration (limiting TEWL) and reducing the itching sensation that would feed the vicious circle of AD.

Generally speaking, the key aspects of a well-formulated dermatological cosmetic product are:

- SIMPLICITY: The number of ingredients is limited (10-20) to those which are strictly necessary
- EFFICACY: Active ingredients are specially chosen for their function and are contained in a carrier which enhances their bioavailability and has a beneficial effect on skin
- SAFETY: Only top-quality raw materials are chosen and there are no potentially hazardous ingredients which can sensitize skin.

For a dermatological product, safety plays an important role. Limiting the number of ingredients in the formulation is key. Below are some categories that we consider particularly critical for a dermatological product and should be avoided:

1. FRAGRANCES

Fragrances used in cosmetic products are easy to identify as they must be included in the list of ingredients under the generic name of PARFUM, according to the European Regulation No. 1223/2009.

Perfumes are referred by the term Perfume, without specifying the composition. The presence of any of the substances commonly found in essential oils and fragrances which are listed in Annex III and have been shown to induce an allergy in epidemiological studies conducted throughout Europe, must be indicated. The presence of these molecules, widely known as allergens, in the product ingredients must be stated in leave-on products (leave-on creams, make-up, sun care products etc.) when concentration is higher than 0.001% and in rinse-off products (cleansers - shampoos) for concentrations higher than 0.01%. Indicating the presence of allergens on the label helps prevent consumers who are sensitive to these substances from coming into contact with products which are not completely safe for them.

Numerous studies have identified increased sensitization to fragrances in AD patients compared to non-AD patients [Simonsen et al., 2017; Lubbes et al., 2017; Cattani et al., 2022]. A recent study found positive reactions to fragrances in 11.8% of cases [Trimeche et al., 2023].

Due to the chemical complexity of the parfume (mixture of molecules) and the increased sensitization, the suggestion is to choose fragrance-free and allergen-free emollients.

2. HEAVY METALS

Metals, mainly nickel, are the most common frequent allergens based on recent literature. In fact, it was suggested that patients with AD have a genetic susceptibility to developing delayed hypersensitivity reactions to metals through Toll like receptor dysfunction and mutations in the filaggrin gene [Malajian et al., 2013].

Heavy metals are prohibited in cosmetic products and are listed in Annex II of Regulation 1223/2009. Traces of heavy metals can be found in colored pigments and/or can be transferred during the production process from the steel in the plant machinery.

The allergens nickel, cobalt and palladium are widely found throughout the population: it is therefore important to check cosmetic products intended for dermatological use after

production to make sure they do not contain nickel or other heavy metals in concentrations higher than those considered to cause sensitization, measured in ppm.

Nickel and other heavy metals do not appear on the list of ingredients as they are prohibited.

To determine their presence as contaminants in traces, the product must undergo specific testing using highly sensitive methods of analysis.

Cosmetic products with levels of heavy metals < 1ppm are considered safe, as the risks of sensitization for the public are considered insignificant.

If, however, someone is already sensitive, they may react to nickel and heavy metals in products even if their levels are below 0.1 ppm.

A recent study has shown that the most frequent sensitizers are metals (nickel sulphate, cobalt chloride, potassium dichromate), covering 45.9% of all 185 positive patch test reactions, followed by fragrances (14.6%) and isothiazolinones (13.5%) [Bonamonte et al., 2022]. Also in several African countries, Nickel, cobalt and potassium dichromate are reported as common allergens [Bonefald et al., 2023].

3. PRESERVATIVES

Preservatives are substances that prevent microbial growth and are added to cosmetic products to ensure their microbiological quality during use.

Legislation states that only the molecules on the positive list of Regulation 1223/2009 (annex V), which also establishes the concentrations for use for the different kinds of products, can be used as preservatives in cosmetic products.

The risk of toxicity is lower for rinse-off products, as the amount of time they come into contact with the skin is very limited compared to leave-on products.

The process for including a molecule in Annex V is long and complex and includes toxicity studies to exclude any potential toxicity for humans and sensitization studies to evaluate the molecule’s ability to sensitize skin.

This procedure, however, is not without its flaws and at times preservatives which have been deemed safe and therefore added to the Annex turn out not to be compliant following epidemiological monitoring carried out after receiving authorization to be released onto the market.

The condition which threatens consumer safety and most commonly appears after using a cosmetic product is contact dermatitis, which can be irritant (ICD) or allergic (ACD).

Epidemiological data on preservatives currently available show the population is highly sensitive to two categories of preservatives: formaldehyde derivatives and thiazolinones.

Isothiazolinones are chemical preservatives widely used in cosmetics, baby wipes, household cleaning products and industrial products.

According to EU Cosmetic Products Regulation (EC) No. 1223/2009, METHYLCHLOROISOTHIAZOLINONE and METHYLISOTHIAZOLINONE are allowed to be used only in rinse off products up to 0.0015% (of a mixture in the ratio 3:1 of 5-Chloro-2-methyl-isothiazol-3(2H)-one and 2-Methylisothiazol-3(2H)-one. They must not be used in the stay-on creams used in AD.

The frequency of contact sensitization to these allergens in patients with AD varies between 1% and 20% in the literature [Akan et al., 2015].

In a recent study regarding contact allergy in AD, it is observed a frequency of 8.6% [Trimeche et al., 2023]. This prevalence is higher than that observed in a earlier Tunisian study (2.2%) and t may be attributed to the increasing prevalence of contact eczema to isothiazolinones over the last decade [Belhadjali et al., 2008; Francuzik et al., 2019]. This reflects their use as preservatives at higher concentrations. Indeed, the maximum authorized concentration is 15 ppm (0.0015%) for methylchlorisothiazolinone/methylisothiazolinone (MCI/MI) (3:1) or 0.01% for methylisothiazolinone (MI) alone, in rinse-off products only, according to European Union legislation. In Tunisia, the study by Belhareth et al. demonstrated the presence of MI in 13.5% of the 870 cosmetic products examined [Trimeche et al., 2023].

Regarding formaldehyde derivates, it was historically used as a preservative in personal care products. However, formaldehyde, in direct contact with the skin, can react with skin proteins and cause an acute inflammatory reaction, which may progress to skin sensitization following repeated exposure.

Formaldehyde and formaldehyde releasers are still widely present in our environment and continue to be important causes of contact allergy and allergic contact dermatitis.

Although in Europe, contrary to the United States, the use of free formaldehyde in cosmetics is nowadays forbidden, mainly due to its carcinogenic properties, it can still be found as a hidden impurity in them. Moreover, formaldehyde can also occasionally be formed de novo from auto-oxidation of ethoxylated alcohols in skincare products. The five most relevant formaldehyde releasers used in cosmetics (in declining order of their potential to release formaldehyde) are: quaternium-15 (although in the EU forbidden since 2019), diazolidinyl urea, dimethyloldimethyl hydantoin (DMDMH), imidazolidinyl Urea, 2-bromo-2-nitropropane-1,3-diol [Goossens et al., 2021].

In Europe, the prevalence of contact allergy has been found to be stable to decreasing in recent years, between 1.5% and 2.5%, yet occasionally somewhat higher figures were reported (eg, ~4%). Instead in the United States, where cosmetic regulations are less stringent and exposure to these chemicals thus more pronounced, contact allergy rates are still high [Goossens et al., 2021].

Phenoxyethanol (EINECS/ELINCS # 204-589-7, also called ethylene glycol monophenyl ether) is positively listed (Annex V/29) to be used up to 1% in Cosmetics (EU Cosmetic Products Regulation (EC) No. 1223/2009). It is widely used as a preservative to limit bacterial growth and is also approved by other expert groups (e.g. CIR).

Microbiological safety is an indispensable requirement, that can also be achieved with the use of alternative preservatives. Indeed, microbiological safety can be guaranteed with alternative methods which do not use preservatives in the formula. This approach is more costly as it involves careful consideration of the FORMULA (choice of ingredients), PACKAGING (use of airless containers which prevent the product from coming into contact with the air during use) and the PRODUCTION PROCESS (production lines which use ultra-pure water or sterile conditions).

The choice of preservative system is therefore crucial to ensure the microbiological safety of the product on the one hand, and to minimize the risk of sensitization on the other.

4. ESSENTIAL OILS and VEGETAL EXTRACTS

Precisely because it is necessary to limit the number of molecules with which the skin comes into frequent contact, we believe that the cosmetic use of essential oils and plant extracts should be avoided. In fact, like fragrances, these raw materials do not consist of a single ingredient but of mixtures of molecules that add complexity and may lead to sensitization.

Hypersensitivity to essential oils is not uncommon, as demonstrated by a recent study conducted by the Information Network of Departments of Dermatology (IVDK) [Geier et al., 2022]. Markers of sensitization to essential oil are complex due to the presence of numerous constituents, including terpenes, sesquiterpene hydrocarbons, alcohols, aldehydes, and phenols. The composition of essential oils can vary significantly between suppliers, and the concentration of haptens may differ depending on the origin, production methods, and storage of the essential oil [Barbaud et al., 2023].

Lavendula officinalis, *Citrus limonum*, *Eucalyptus citriodora*, *Pelargonium graveolens*, *Mentha piperita*, *Cinnamomum zeylanicum bark oil*, *Lavandula hybrida*, *Eugenia caryophyllus flower oi*, and Turpentine oil have been categorized as established contact allergens in humans according to Uter. Based on the literature also tea tree oil could be considered as an essential oil human sensitizer. Tea tree oil is not only used as an essential oil but also as a cosmetic ingredient in antiperspirants [Uter et al., 2013; Barbaud et al., 2023].

Oxidized fragrance molecules, which can be present in essential oils, are known to be irritating and can further disrupt the compromised skin barrier of individuals with AD. Given these considerations, it is advisable to **recommend against the use of essential oils in individuals with a history of AD** [Christensson et al., 2009; Barbaud et al., 2023].

5. OTHERS

Again, based on the principle of limiting the number of ingredients in the formula, **colorants** should be avoided. In fact, they bring no benefit whatsoever to the atopic patient, but increase formulation complexity without a valid scientific reason.

Similarly, ingredients that may compromise the skin barrier should be avoided in a patient who already has skin changes. One of them is **denatured alcohol at high levels**.

Finally, all those ingredients that do not belong to the above-mentioned classes, but which may widely induce sensitization should be avoided, such as, lanolin or wool alcohol, *Myroxylon pereirae* resin (balsam of Peru), Triclosan, Chlorhexidine.

In conclusion, patients with AD may be affected by contact allergy that contributes to the maintenance and aggravation of their dermatosis. This is due to the damaged skin barrier (higher chance of allergen penetration) and long-term local therapy, that can be increase the risk of developing a contact hypersensitivity.

Although only a few studies on contact allergy in African countries have been published, a recent review provide an overview of the most common contact allergens identified using patch tests in African countries based on a review of the existing literature. Nickel, cobalt, chromium, fragrance mix and p-tert-butylphenol-formaldehyde resin were the dominating contact allergens responsible for 40%–90% of the positive patch test reactions [Bonefeld et al., 2023]. A recent study of children with AD in African region has shown that among the AD patients paraben mix, methyldibromoglutaronitrile (MDBGN), fragrance mix and cobalt

chloride were the commonest sensitisers [Ibekwe et al., 2023]. The prevention, avoidance, and regulation of reliably identified contact allergens could reduce the disease burden of ACD considerable in some African countries. This becomes particularly crucial for those people who have an impaired skin barrier and require very frequent and constant use of emollients.

While we have so far discussed the ingredients that should be avoided in an emollient for subjects with AD to ensure its safety, there is also **the aspect of efficacy to consider**.

Dry and damaged skin must be treated daily with emollient creams which reduce or alleviate the discomfort common to this condition. Dry skin can be successfully treated with **emollients**, lipid substances which create an occlusive film over the surface of the skin and restrict transepidermal water loss (TEWL), increasing the lipid content of the stratum corneum. These lipids are normally carried in an emulsion which makes their application easy and pleasant, especially on widespread areas of the body.

Based on the literature, we list below the ingredients or categories of ingredients that we consider to be beneficial for atopic skin:

- **Essential lipids of the epidermal barrier**: this category includes ceramides, cholesterol and fatty acids. These molecules (lipids) make up the intercellular cement that holds the bricks of the stratum corneum together, namely the epidermal cells. Ceramides can improve both permeability barrier function and stratum corneum hydration [Elias et al., 2022].

- **Oils**: in cosmetics, many molecules belong to the class of oils, even though they are very different from a chemical point of view and have different functions and sensory effects on the skin. The most effective emollients for dry skin or AD are hydrocarbons, for example paraffinum liquidum; mineral, animal and vegetable waxes like microcrystalline wax, beeswax or carnauba wax; certain vegetable oils, which are enriched in essential fatty acid, linoleic acid or gamma-linolenic acid [Elias et al., 2022]. It is fundamental to check the quality of the vegetable oils, such as the stability, peroxide value, iodine value and acidity. The quality control is fundamental for each batch, to achieve a good grade of standardization.

- **Glycerin:** humectants, such as glycerin, can bind and hold water providing effectively moisturization to the skin [Danby et al., 2020]. Moreover, glycerol for instance significantly accelerates skin barrier recovery when applied to the skin following disruption [Fluhr et al., 1999; Atrux-Tallau et al., 2010]

- **Urea:** is widely used in dermatology to improve skin barrier function and as one of the most common moisturizers and keratolytic agent. It plays a fundamental role in regulating keratinocyte proliferation, the skin’s barrier function and antimicrobial defense. Urea induces the expression of filaggrin and loricrin, genes which are important for keratinocyte differentiation. Formulation with urea have shown significant clinical improvement in many of the dermatoses presenting with scaly and dry skin such as AD and xerosis. Low concentration is indicated for moisturizing and optimizing the skin’s barrier function [Piquero-Casals et al., 2021].

- **For an emollient to be an effective adjuvant, it must be applied regularly. This is why it must be safe, effective, affordable, usable and simple in terms of the number of ingredients, especially when the skin barrier is compromised, such in AD. The detailed formula for Canoderm which is advocated as the prototype**

of recommended urea-based moisturizers in this application is as follows, showing that some ingredients have several functions, and that the formula fulfills the principles given for safety (limited to13 ingredients) and efficacy.

- **Key Ingredients: Urea** *(natural moisturizer)* **Lactic Acid** (*natural moisturizer, exfoliant*)
- **Other Ingredients by function:**
- ***Buffer*****:** Lactic Acid
- ***Emollient***: Cetostearyl Alcohol, Hydrogenated Canola Oil, Dimethicone, Glyceryl Stearate
- ***Emulsifyier:*** Polysorbate 60, Cetostearyl Alcohol, Glyceryl Stearate
- ***Moisturizer/humectant*****:** Urea, Propylene Glycol, Lactic Acid
- ***Scent****:* Hard Paraffin
- ***Preservative*****:** Ethyl Parahydroxybenzoate (E 214), Methyl Parahydroxybenzoate (E 218)
- ***Solvent:*** Propylene Glycol, Purified Water
- ***Surfactant/cleansing***: Polysorbate 60, Cetostearyl Alcohol
- ***Viscosity controlling***: Cetostearyl Alcohol, Hydrogenated Canola Oil, Carbomer, Hard Paraffin, Glyceryl Polymethacrylate
-

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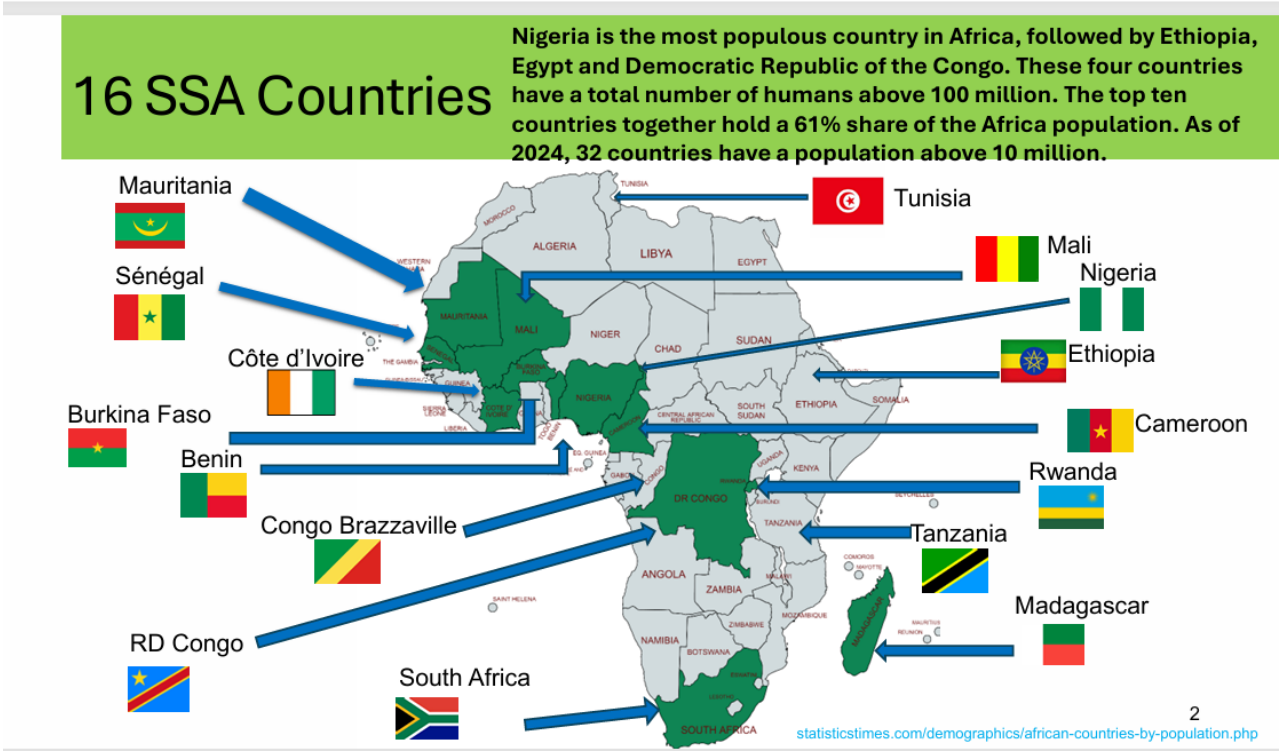
ANNEX 3: Doha Report ASDV ISAD on the accessibility of emollients in AD in SSA.

A report on the accessibility of emollients in AD in SSA- to ISAD-WHO Meeting in Doha, Qatar

Erere Otrofanowei (Nigeria) for African AD Working Group.



Population

MDGRr	DRC	Burkina Faso	SNG	Bénin	NGR	Rwanda	MAURIT	CMR	Ethiopia	Tunisia	SA	CD'V
30.325.732	102 million	22.752.315	18 032 473	13.352.864	227.143.814	13.246.394	4 244 878	27.912.000	129 million	12,458,223	61,020,221	29 389 150

- **Madagascar is the only island in these countries. It is the fourth-largest island in the world**
- **Nigeria has the largest population by far, with over 227 million people, followed by the Ethiopia with over 129 million.**
- **Mauritania has the smallest population among these countries, with approximately 4.2 million people**
- **All the countries are facing the challenge of poverty, healthcare access and education**

Mali 22.593.485

3

Drugs for AD available: traditional emollients

Madagascar	RD Congo	Senegal	Burkina Faso	Bénin	Nigeria	Rwanda	Mauritania	Ethiopia	Cameroon	Cd'V
Coconut oil	Coconut oil Beef marrow Shea butter Palm kernel oil Palm oil	Almond Oil	Trafaderma lait	Coconut oil Shea butter **Mali: Shea butter**	Coconut oil Shea butter	Ghee = Beurre clarifie	Shea butter	Butter	Coconut oil Shea Butter	Shea butter

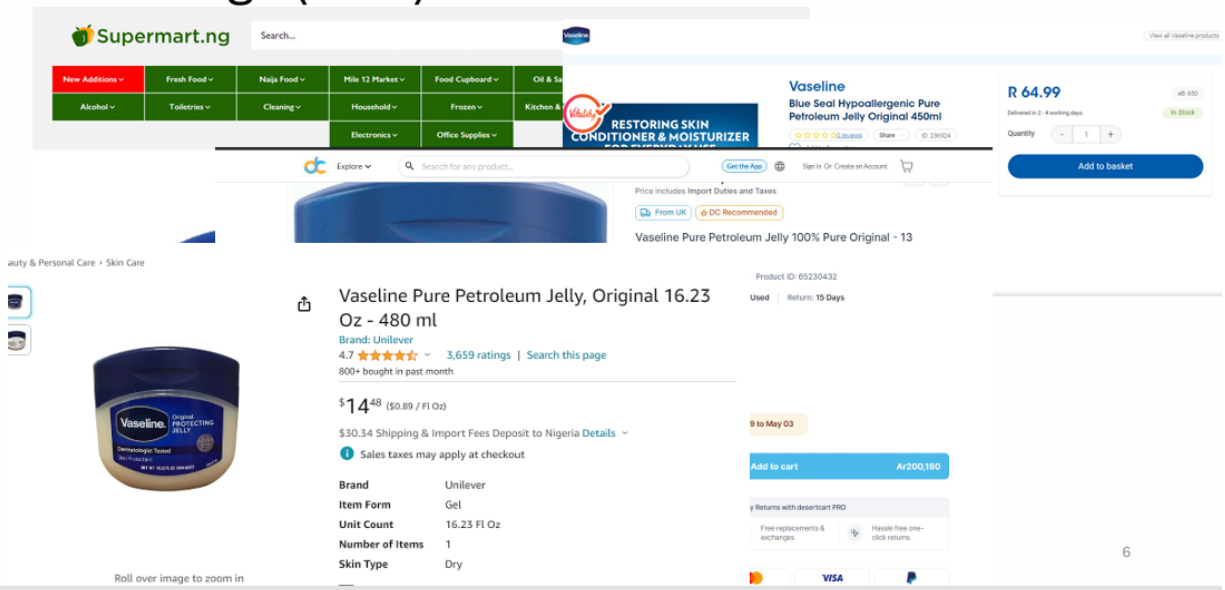
- **Coconut oil and shea butter are the most frequent traditional emollients used due to the ease of production and availability**

Industrial emollients(1)

Madagascar	RD Congo	Senegal	Burkina Faso	Bénin	Nigeria	Rwanda	Mauritania	Cameroon
*Vaseline cream *Dexeryl cream *Topicrem DA baume emollient *Cerave baume hydratant *Cerave lait hydratant	White vaseline 35gm Dexeryl 250g : Urelia creme 150ml : Topicrem baume 200ml Topicrem baume 500ml	Vaseline cream *Dexeryl cream *Topicrem DA baume emollient *Cerave baume, lait hydratant, crème mousse nettoyante *Topicrem	Atoderm creme 500ml Atoderm creme 200ml Atoderm intensive baume 500 ml Atoderm pain	*Cerave crème moussante nettoyante *Topicrem DA baume emolliente visage corps *Topicerm ultra hydratant lait corps	Topicrem DA Baume Topicrem Cica Bioderma Atoderm Intensive Baume Lipikar AP Baume, 50 CeraVe Baume Olay Lotion Shea Butter vit	Topicrem DA baume emollient Topicrem UR-10 crème lissante anti-rugosites Topicrem lait unifiant ultra-hydratant Sebamed lait	Vaseline Pde 500g : Lipikar Baume, Gel, Pain surgras Dexeryl cream Topicrem DA baume emollient Cerave baume hydratant	-Lipikar Baume AP+ 400ml- -Lipikar Syndet AP+ 400ml- -Cerave Baume 454g- -Cerave crème lavant- -Rilastil Aqua 400ml- -Rilastil Xerolact 400ml-

5

The range (cost) of emollients/moisturisers



6

MINIMUM WAGE IN PARTICIPATING COUNTRIES

	TANZANIA	MAURITIANA	BURKINA FASO	SENEGAL	MADAGASCAR	COTE D'IVOIRE	CONGO BRAZZAVILLE	NIGERIA	TUNISIA	RD CONGO	MALI	ETHIOPIA	CAMEROON	BENIN	RWANDA	SOUTH AFRICA
Minimum wage	TZS 140,000	MRU 45,000.	F CFA 45,000	F CFA 237/Hr 40,000/ month	MGA 262,680	F CFA 39,960 F CFA 75,000	FCFA 120,000	NGN 65,000	TND 417.558	CDF 7,075	F CFA 40,000	ETB 420	FCFA 43,969	F CFA 52,000	RWF100/day 56,000 averag	R27,58/hr 4.543.44/month
1 dollar/ currency	1/ 2725	1/39.52	1/603	1/603	1/4571	1/603	1/603	1/1,633	1/3.09	1/2,841	1/603	1/119	1/603	1/603	1/1,355	1/17.65
Salary in dollar	51.4	1,138	74	66	57	124	199	39	135.132	2.4	74	3.5	72.9	86	41	257
% cost of Vaseline/salary	9.7%	0.4%	6.7%	7.6%	8.75%	4.02%	2.5%	12.8%	3.69%	207%	6.7%	140%	6.8%	5.8%	12.17%	1.9%

Vaseline is 4.99 dollars for 1 on Amazon

Some countries have different Minimum wages for different Sectors

South Africa, Senegal pay/hour. Monthly pay has been calculated Using a basic 40-hour week.

wageindicator.org

ANNEX 4. Letters of Support

ASDV
AFRICAN SOCIETY OF DERMATOLOGY & VENEREOLOGY
SOCIÉTÉ AFRICAINE DE DERMATOLOGIE ET VÉNÉRÉOLOGIE
www.asdvafrica.org

Secretariat
C/o Dr Perpetua Ibekwe
Department of Medicine, Faculty of Clinical Sciences, University of Abuja
Gwagwalada, Abuja, Nigeria
Email: info@asdvafrica.org
Phone: +234(0)8033192661

Supported By

October 12, 2024

Prof Alain TAIEB
President ISAD
https://www.isad.org/

LETTER OF SUPPORT

Dear Prof TAIEB,

On behalf of the African Society Dermatology and Venereology (ASDV), we are pleased to extend our official support to the International Society of Atopic Dermatitis (ISAD) on the application for the 2025 revision of WHO Essential Medicines Core List.

As the premier association for dermatology and venereology in Africa, ASDV is dedicated to promoting best practices, improving patient outcomes and advancing medical knowledge across the continent.

We recognize the importance of the use of affordable and good quality emollients for the management of atopic dermatitis especially in low resource settings such as ours.

We strongly support ISAD efforts to ensure patients with atopic dermatitis receive the best quality of care.

Thank you

Your Sincerely,

Professor Abel Onunu
President,

Dr Perpetua Ibekwe
Secretary-General,

AFRICAN SOCIETY DERMATOLOGY AND VENEREOLOGY

International Alliance of Dermatology Patient Organizations
GLOBALSKIN.ORG

October 30, 2024

WHO Expert Committee on the Selection and Use of Essential Medicines
World Health Organization
Geneva, Switzerland

Subject: Support for Inclusion of Moisturizers for Atopic Dermatitis in the WHO Essential Medicines List

Dear Members of the Expert Committee,

I am writing on behalf of the International Alliance of Dermatology Patient Organizations (GlobalSkin), a unique global alliance of 280+ patient organizations located in 70 countries, committed to improving the lives of patients worldwide, including those affected by atopic eczema (also known as atopic dermatitis) and related skin conditions. We fully support the application for the inclusion of moisturizers for the care of atopic dermatitis in the WHO Essential Medicines List, particularly for low-resource countries.

Atopic dermatitis is a chronic inflammatory skin condition that affects millions of people worldwide, often leading to severe discomfort, stigma, and diminished quality of life. In many low-resource settings, access to effective and affordable treatments remains a significant barrier. Moisturizers are a cornerstone of atopic dermatitis management, providing essential hydration and helping to maintain the skin barrier, which is crucial for preventing flare-ups and complications.

The inclusion of moisturizers in the Essential Medicines List would ensure that these vital products are accessible to those who need them most. Many families in low-resource settings lack access to basic skincare products, and the financial burden of acquiring even the simplest moisturizers can be overwhelming. By making these essential treatments more widely available, we can help reduce the suffering associated with this condition and improve overall health outcomes. Furthermore, the promotion of moisturizers as essential medicines aligns with the WHO's commitment to universal health coverage and health equity. Ensuring that effective and affordable treatments are available to all, regardless of socioeconomic status, is essential in our global efforts to address health disparities.

We urge the WHO to consider the significant impact that the inclusion of moisturizers for atopic dermatitis would have on affected individuals, their families, and communities in low-resource countries. By endorsing this application, you can play a crucial role in transforming lives and promoting better health outcomes for those living with this challenging condition.

Thank you for your attention to this important matter. We stand ready to support your efforts in improving access to essential treatments for atopic dermatitis patients.

Sincerely,

Jennifer Austin
Chief Executive Officer

INTERNATIONAL ALLIANCE OF DERMATOLOGY PATIENT ORGANIZATIONS | 43 FLORENCE STREET | OTTAWA ON K2P 0W6 | CANADA

International League of Dermatological Societies
Skin Health for the World

29 October 2024

WHO Expert Committee on the Selection and Use of Essential Medicines
World Health Organization
Geneva, Switzerland

Dear Members of the Expert Committee,

On behalf of the International League of Dermatological Societies, I am pleased to express our strong support for the application submitted by the International Society of Atopic Dermatitis to include urea- and glycerol-based topical moisturisers on the WHO Model List of Essential Medicines (EML) and Model List of Essential Medicines for Children (EMLc) for the treatment of atopic dermatitis in both adults and children.

The International League of Dermatological Societies, representing over 215,000 dermatologists and 217 member organisations across 103 countries, including many in the African region, advocates for safe, effective, and affordable dermatological care. The need for accessible emollients in treating atopic dermatitis is especially critical in low-resource settings, as highlighted by recent surveys in Sub-Saharan Africa and frequent requests from dermatologists in the WHO-AFRO region who lack reliable access to moisturisers for their patients.

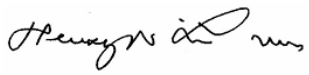
Including urea- and glycerol-based emollients in the EML and EMLc would provide a safe, effective way to improve skin hydration and barrier function, which is essential for managing and preventing symptoms of atopic dermatitis. Accessible moisturisers would reduce the likelihood of secondary infections in patients with atopic dermatitis, supporting physical and mental well-being, especially in resource-limited settings where treatment options are scarce.

By prioritising these emollients as essential medicines, the Committee would significantly advance global skin health, improve quality of life, and alleviate the healthcare burden of atopic dermatitis, particularly in underserved regions. This inclusion would enhance access to effective treatments for patients of all ages suffering from this challenging condition.

We respectfully urge the Committee to consider this essential inclusion in line with WHO's goals to address urgent health needs and improve health equity for all.

Thank you for your consideration.

Yours sincerely,



Prof. Henry W. Lim
President, International League of Dermatological Societies (ILDS)