

A.30 Urea- and glycerol-based topical moisturizers – EML and EMLc

Reviewer summary

☐ Supportive of the proposal

☒ Not supportive of the proposal

Justification (based on considerations of the dimensions described below):

High quality uptodate evidence synthesis is needed

Medicine:

The submission proposes the inclusion of one carbamide-based (5% urea) and two glycerol (15% and 20%) -based moisturizer creams registered for the indication dry skin in patients diagnosed with AD in the core list of the EML and EMLc

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 applicants “recognize the critical importance of the excipients in moisturizers for the final safety, efficacy and cosmetic attributes”.

Applicants 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.

Efficacy:

Evidence to support overall efficacy

Out of the summarized systematic reviews, three are relevant for the comparison of moisturizers to no moisturizers (2-5). These 3 systematic reviews appear to be of varying quality, but the applicants did not assess them using tools such as AMSTAR.

The most reliable one in terms of methodology appears to be the Cochrane review (3) although it searched up to 2015, indicating it is 10 years old. Also, it lumped all moisturizers for most analyses. It found:

- Moisturizer vs. no moisturizer: improvement in eczema severity: lower SCORAD: MD -2.42, (-4.55 to -0.28) indicating no effect considering the MID of 8.7.
- investigator-assessed disease severity was improved; certainty rated as high although the CI for the SMD crosses thresholds of clinical significance indicating imprecision
- flare was improved
- patients experienced improvement from treatment (table 5): results show imprecision, heterogeneity, and high risk of bias or unclear risk of bias (particularly for the studies showing the largest improvements); certainty of evidence was assessed as very low

The most recent systematic review (Sidbury 2023; #4) lumped all non-prescription moisturizers and found:

- moisturizers were associated with improvement as measured by SCORAD or EASI (SMD of 0.51, 95% CI: 0.17-0.85). these results indicate both a small effect and a bit of imprecision indicating the possibility of either no effect and moderate effect (so low certainty evidence by my judgement as opposed to the author’s moderate certainty)
- other outcomes reported as favorable, but certainty rated seemed inflated (at least imprecision and heterogeneity seemed as not properly accounted for) (reference to figures under table 6 in the application)
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Evidence for the moisturizers recommended for EML listing emollients

The Cochrane systematic review (again 10 years old) concluded based on 4 studies that urea-containing cream compared with no such cream was associated with:

- Skin improvement (1 study, 129 participants; RR 1.28, 95% CI 1.06 to 1.53; low-quality evidence)

	<ul style="list-style-type: none"> • Comparable satisfaction (1 study, 38 participants; low-quality evidence) • Improved dryness (physician assessment) (1 study, 128 participants; RR 1.40, 95% CI 1.14 to 1.71; moderate-quality evidence) • Fewer flares (1 study, 44 participants; RR 0.47, 95% CI 0.24 to 0.92; low-quality evidence) • quality of life were not addressed <p>The Cochrane systematic review (again 10 years old) concluded based on 4 studies that glycerol-containing cream compared with no such cream was associated with:</p> <ul style="list-style-type: none"> • Skin improvement (1 study, 134 participants; RR 1.22, 95% CI 1.01 to 1.48; moderate-quality evidence) • investigator-assessed SCORAD scores (1 study, 249 participants; MD -2.20, 95% CI -3.44 to -0.96; high-quality evidence); however SCORAD MID was reported to be 8.7 making this non a meaningful improvement • Participant satisfaction and quality of life were not addressed <p><i>possible small benefit, but this is a judgment made with limited confidence given the lower certainty of the evidence and given it is not based on a high quality up to date systematic review</i></p> <p>Safety:</p> <p>The Cochrane systematic review (10 years old) concluded that urea-containing cream compared with no such cream was associated with:</p> <ul style="list-style-type: none"> • More adverse events reported (1 study, 129 participants; RR 1.65, 95% CI 1.16 to 2.34; moderate-quality evidence); NNTH = 4 <p>The Cochrane systematic review (10 years old) concluded that glycerol-containing cream compared with no such cream was associated with:</p> <ul style="list-style-type: none"> • No difference in adverse events. <p><i>possible small harm, but this is a judgment made with limited confidence given the lower certainty of the evidence and given it is not based on a high quality up to date systematic</i></p> <p>Special requirements:</p> <p>vehicles and excipients may be harmful</p> <p>Reported they can be used during pregnancy and lactation</p> <p>this is particularly relevant give the need for long term use</p> <p>Balance:</p> <p><i>Possibly in favor of both compounds, but this is a judgment made with limited confidence given the lower certainty of the evidence and given it is not based on a high quality up to date systematic</i></p> <p>Budget issues:</p> <p>cost seems to vary but reasonable in most settings</p> <p>No cost effectiveness information included</p> <p>Regulatory approval: not universally approved or accessible</p>
<p>Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives?</p> <p>(https://list.essentialmeds.org/)</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Not for the proposed indication</p>
<p>Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication?</p> <p>(e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Not applicable</p>

25th WHO Expert Committee on Selection and Use of Essential Medicines
Expert review

<p>Does adequate evidence exist for the safety/harms associated with the proposed medicine?</p> <p>(e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Not applicable
<p>Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Not applicable
<p>Are there any special requirements for the safe, effective and appropriate use of the medicines?</p> <p>(e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable
<p>Are there any issues regarding price, cost-effectiveness and budget implications in different settings?</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable
<p>Is the medicine available and accessible across countries?</p> <p>(e.g. shortages, generics and biosimilars, pooled procurement programmes, access programmes)</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable
<p>Does the medicine have wide regulatory approval?</p>	<input type="checkbox"/> Yes, for the proposed indication <input type="checkbox"/> Yes, but only for other indications (off-label for proposed indication) <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable