## A.7 Ciclopirox – EML

**Reviewer summary**

☐ Supportive of the proposal

☒ Not supportive of the proposal

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

- **Public health relevance**
  1. **Onychomycosis accounts for half of all nail disease cases. Global prevalence of onychomycosis is ~10% a**nd can go up to 48% in countries. **The prevalence was ⩾ 20% in adults 60 years or older and ⩾ 50% in adults 70 years or older.**
  2. Unfortunately, onychomycosis is difficult to treat, as indicated by high rates of treatment failure and recurrence (up to 53%) probably associated with antifungal resistance and the formation of dormant fungal cells by the pathogen.
- **Evidence of comparative efficacy and safety**
  - **Ciclopiro**x is an hydroxypyridone derivative with antimicotic activity against a very broad spectrum of microorganism, as it inhibits dermatophytes, yeasts (including certain frequently azole-resistant Candida species) and non-dermatophyte moulds, as well as bacteria (particularly beneficial in the treatment of mixed infections).
  - **Ciclopirox is classified as "other antifungals for topical use**". Topical antifungals (ciclopirox 8%, efinaconazole 10%, and tavaborole 5%) are recommended to treat mild-to-moderate onychomycosis. Since the recurrence rate of onychomycosis is high, older patients perhaps consider using a topical antifungal as long-term maintenance therapy one to three times per week to prevent the recurrence of onychomycosis or to treat early disease.
  1. **The 2020 Cochrane Systematic Literature Review (SLR) of topical and device-based treatments for fungal infections of the toenails：** Overall, when assessing complete cure, moderate-quality evidence supports ciclopirox 8% HPCH hydrolacquer, whereas low-quality evidence supports ciclopirox 8% water insoluble lacquer. For the newer tavaborole lacquer, effectiveness is supported by moderate-quality evidence, while high-quality evidence supports the recently available efinaconazole.
  2. **Head-to-head clinical trials：** Ciclopirox 8% HPCH hydrolacquer was proved to be significantly superior to both lacquers (amorolfine and ciclopirox 8% water-insoluble) and placebo in terms of efficacy.
  3. **Real World Evidence (RWE):** Treatment combinations of ciclopirox 8% HPCH with oral anti-fungal agents were commonly used in the Spanish clinical practice setting and time to response was unrelated to the type of oral antifungal agent.
  4. **In vitro and in vivo studies:** Ciclopirox 8% HPCH hydrolacquer provides faster and larger penetration compared to ciclopirox and amorolfine water insoluble formulations.
  5. **Clinical Development Program:** Ciclopirox 8% HPCH hydrolacquer is **more active and better tolerated than reference** ciclopirox 8% water insoluble lacquer in the long-term treatment of onychomycosis. (1) Ciclopirox 8% HPCH hydrolacquer is proven to be statistically **more effective in treating mild-to-moderate onychomycosis** compared to placebo at week 48 and statistically more effective than both placebo and water-insoluble ciclopirox 8% lacquer at week 60 in terms of complete cure rate, a composite efficacy endpoint difficult to achieve (100% clear nail, negative KOH microscopy, and negative culture). (2) Ciclopirox 8% HPCH hydrolacquer is also proven to be **significantly superior to placebo at week 48 in rate to conversion culture and response rate**, and **significantly superior to both placebo and reference ciclopirox 8% water-insoluble lacquer in terms of response rate at week 60**. (3) **Safety profile is better** than that of the reference water insoluble lacquer.
  6. **Ciclopirox has low propensity to induce anti-fungal resistance.**
  7. **Recommendations in current clinical guidelines: (1)** No onychomycosis specific guidelines have been published by the WHO.(2) **The use of topical ciclopirox (both HPCH hydrolacquer and water insoluble lacquer) for the treatment of mild-moderate onychomycosis, or as an adjuvant to systemic treatments, is recommended by some international and national guideli**nes and scientific articles.
- **Cost and cost-effectiveness considerations**

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| | 1. In 17 out of the 20 countries analyzed, ciclopirox is the cheapest option (dominant) among the antifungal lacquers available in each market. Out of the 17 countries were ciclopirox was dominant, in 11 it was due to ciclopirox 8% HPCH formulation.<br>2. In 14 out of the 20 countries analyzed, the formulation of ciclopirox 8% HPCH is the only available or the cheapest among other ciclopirox formulations.<br>3. No studies evaluate the cost or cost-effectiveness of ciclopirox 8% HPCH hydrolacquer relative to other topic medicines for treatment of Onychomycosis.<br>➢ **Any other issues that may be relevant in determining the status of a medicine as 'essential' (e.g., recommendations in WHO guidelines, feasibility of use, diagnostic requirements, availability, access).**<br>1. Pharmacopeial standards for Ciclopirox are available in European Pharmacopoeia (Edition 11.0) and US Pharmacopeia (USP 31st revision).<br>2. Ciclopirox without HPCH excipient is available in 33 countries worldwide, and in **19** out of these 33, **ciclopirox 8% HPCH is also available**.<br>3. There are 20 countries additional in the world where the only ciclopirox formulation available is 8% HPCH.<br><br>**Recommendation: Onychomycosis is a common nail disease globally. Global prevalence of onychomycosis is ~10% and can go up to 48% in countries.** Treatment of onychomycosis is challenging in practice because prolonged treatment (12-18 months with oral antifungal agents: fluconazole or griseofulvin) is commonly associated with treatment failures and relapses.<br><br>**Ciclopirox 8% HPCH hydrolacquer is indicated for the treatment of mild to moderate fungal infections of the nails caused by dermatophytes, yeasts and moulds, without nail matrix/lunula involvement in adult patients by regulatory authorities in some countries**, given that its activity against dermatophytes, yeasts and non-dermatophyte moulds, as well as bacteria. **Ciclopirox 8% HPCH hydrolacquer provides faster and larger penetration** compared to ciclopirox and amorolfine water insoluble formulations, and **well tolerated**. **Some international and national guidelines and scientific articles recommend the use of topical ciclopirox** (both HPCH hydrolacquer and water insoluble lacquer) as topical therapy for mild to moderate onychomycosis active treatment alone or in combination with oral antifungal agent and for prophylaxis in the post-treatment phase for patients that have achieved cure in the active treatment. **However, the efficacy in treating mild-to-moderate onychomycosis was based on combined therapy with oral antifungal. So far, no studies evaluating the cost or cost-effectiveness of ciclopirox 8% HPCH hydrolacquer** relative to other comparators for treatment of Onychomycosis are available.<br><br>**There are no medicines currently included in the EMLs indicated specifically for onychomycosis.** In clinical practice, topic use of antifungals is common for dermatologic diseases. **I suggest listing at least one representative topic antifungal class in the EML for the treatment of onychomycosis, which is a common dermatologic disease in adults.** But I am not sure using ciclopirox 8% HPCH hydrolacquer alone is the best choice for mild-moderate onychomycosis in terms of efficacy, price, cost-effectiveness because the evidence is limited. **So, I reserve my recommendation at this time.** |
| Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives?<br><br>(**https://list.essentialmeds.org/** ) | ☐ Yes ☒ No ☐ Not applicable |
| Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication?<br><br>(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;) | ☒ Yes ☐ No ☐ Not applicable |

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Expert review

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| Does adequate evidence exist for the safety/harms associated with the proposed medicine?<br><br>(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;) | ☒ Yes ☐ No ☐ Not applicable |
| Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms? | ☒ Yes ☐ No ☐ Not applicable |
| Are there any special requirements for the safe, effective and appropriate use of the medicines?<br><br>(e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc) | ☐ Yes ☒ No ☐ Not applicable |
| Are there any issues regarding price, cost-effectiveness and budget implications in different settings? | ☒ Yes ☐ No ☐ Not applicable |
| Is the medicine available and accessible across countries?<br><br>(e.g. shortages, generics and biosimilars, pooled procurement programmes, access programmes) | ☐ Yes ☒ No ☐ Not applicable |
| Does the medicine have wide regulatory approval? | ☐ Yes, for the proposed indication<br>☐ Yes, but only for other indications (off-label for proposed indication)<br>☒ No ☐ Not applicable |