A.20 Moxidectin – EML and EMLc

Reviewer summary

☐ Supportive of the proposal

☒ Not supportive of the proposal

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

- **Public health relevance**

  Onchocerciasis and lymphatic filariasis caused affect hundreds of millions of people worldwide. Onchocerciasis is associated with severe visual impairment and skin disfigurement. In 2021, onchocerciasis was responsible for the loss of 1.26 million DALYs. Lymphatic filariasis can result in debilitating irreversible lymphoedema and hydrocele. WHO has ranked lymphatic filariasis as one of the world's leading causes of permanent and long-term disability. In 2021, the prevalence of lymphatic filariasis was measured as 56.9 million, responsible for the loss of 1.31 million DALYs. Both conditions primarily affect impoverished populations in tropical regions and are co-endemic in many regions of Africa, resulting in serious social and economic consequences.

  The WHO roadmap for neglected tropical diseases, 2021–2030, has identified onchocerciasis as a disease targeted for elimination (interruption of transmission) and lymphatic filariasis for elimination as a public health problem.

- **Evidence of comparative efficacy and safety**
  1. **Moxidectin is indicated for the treatment of onchocerciasis and lymphatic filariasis** in adults and potentially approved for use in children aged 4 years and older. Moxidectin for onchocerciasis and scabies was included as one of paediatric priority formulations for five neglected tropical diseases by WHO GAPf PADO initiative, reinforcing the public health need for this population.
  2. All available data on Moxidectin for treatment of onchocerciasis and lymphatic filariasis indicate superior efficacy and similar safety to ivermectin in adults and adolescents.
  3. Two RCTs conducted in onchocerciasis-infected **adults and adolescents** met the criteria for inclusion in the systematic review. (1) **Efficacy:** Pooled analysis showed i**ncreased odds in skin microfflariae clearance post-treatment in the Moxidectin group** compared with the ivermectin group (OR: 2.81; 95% CI: 0.95–4.68; moderate quality of evidence). **The efficacy of Moxidectin 8 mg was statistically significantly superior than 150 µg/kg ivermectin** at 6 and 12 months post-treatment. (2) **Safety:** Pooled analysis showed **no significant difference in the occurrence of AEs** among community members post-treatment between the Moxidectin and ivermectin groups (OR: 0.43; 95%CI: -1.64 to 2.5; medium quality of evidence).
  4. A clinical trial NCT04410406 being conducted in Côte d'Ivoire to assess the safety and efficacy of **Moxidectin combination treatments** *versus* **ivermectin combination treatments for Bancroftian Filariasis in 164 adults**. **All treatment regimens were well tolerated and no difference in safety parameters between regimens that contained ivermectin or Moxidectin.** The unpublished preliminary efficacy data strongly suggest that **Moxidectin is superior to ivermectin** and comparable to the diethylcarbamazine-containing regimens (which cannot be used in most of Africa) for clearance of *W. bancrofti microfilaremia* and inactivation of adult worm nests at 24 months.
  5. Unpublished data. (1) Data from Ghana study MDGH-MOX-1006 indicate that **6 mg Moxidectin in children 8-11 years** and **4 mg in children 4-7 years** achieved **comparable Mean (±SD) Plasma Concentrations over time** to **8 mg in adolescents 12-17 years and adults**. The safety of single dose Moxidectin compared to single dose ivermectin is under assessment in participants 4 years and older in the Democratic Republic of Congo and Côte d'Ivoire.
- **Cost and cost-effectiveness considerations**
  1. **There is currently no price for Moxidectin**. MDGH, a not-for-profit pharmaceutical company, is committed to making **Moxidectin tablets 2 mg, available at production costs plus a cost to cover administrative expenses for use in LMIC**s to ensure the sustainability. The cost of Moxidectin production is de-linked from the financing of its development. **At the current production capacity of 1.9 million treatments per year**, **the proposed price for Moxidectin per 8 mg dose (4 x 2 mg tablets) will be US$1.56.**
  2. The declared market value of the **Merck-donated Ivermectin treatment is US$4.50 per treatment**. **The retail market prices may vary significantly**. Ivermectin tablets can be

purchased from various sources, including a WHO prequalified supplier such as Edenbridge, with a declared value of US$83.00 for 20 ivermectin 3 mg Tablets (US$4.15/tab). **A generic ivermectin was estimated to be US$0.70 for a 9 mg dos**e. An ivermectin 3 mg tablet costs US$8.18 in Australia (according to the Pharmaceutical Benefit Scheme website), or US$2.36 per tablet in France (as per the Health Insurance website).

3. Recent modelling suggests that **using Moxidectin could reduce the number of MDA** (mass drug administration) **cycles needed to reach disease elimination**. As a result, the overall programmatic costs for MDA over the reduced time period could also be significantly reduced, compared with current Ivermectin MDA.

- **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).**

1. **The 2017 WHO guideline recommended MDA preventive chemotherapy strategy for lymphatic filariasis elimination.** The MDA regimens include ivermectin (200 µg/kg) in combination with albendazole (400 mg) / diethylcarbamazine citrate (DEC) (6 mg/kg), depending on the co-endemicity of lymphatic filariasis with other filarial diseases.
2. **There is currently no WHO treatment guideline published for onchocerciasis**. **The WHO webpage recommends treating onchocerciasis with ivermectin at least once yearly for 12 to 15 years.**
3. **Moxidectin is not yet included in WHO and national guidelines in endemic countries**. The WHO guideline development group is currently reviewing the available evidence to support the development of guidelines on Moxidectin for the treatment of onchocerciasis and lymphatic filariasis.
4. Moxidectin finished product is **an immediate-release uncoated tablet for oral use containing 2 mg of Moxidectin** which is manufactured to current GMP standards. **Moxidectin has been approved by the US FDA for the treatment of onchocerciasis due to *O. volvulus* in patients aged 12 years and older.** So far, Moxidectin is only available in the US.

Recommendation: Onchocerciasis and lymphatic filariasis cause socioeconomic burden and public concern in endemic countries. The 2021-2030 WHO roadmap for neglected tropical disease has identified onchocerciasis as a disease targeted for elimination and lymphatic filariasis for elimination as a public health problem. WHO recommended annual ivermectin-containing preventive chemotherapy strategy for lymphatic filariasis elimination and ivermectin-based regimen for onchocerciasis treatment. **Moxidectin is one of the promising alternative treatments for accelerating onchocerciasis elimination in endemic countries. The current available RTC trails have shown similar safety profile with increased efficacy in suppressing skin microfilariae compared to ivermectin.** The results are meaningful for interrupting or reducing transmission. **Another appealing advantage for Moxidectin is that Moxidectin product is an immediate-release uncoated tablet (2mg) for oral use. As a child-friendly formulation, availability of Moxidectin can meet the need for children.**

Given the two major advantages of Moxidectin and the WHO priority targets for the elimination of onchocerciasis and lymphatic filariasis**, including Moxidectin in the EML/EMLc should be seriously considered.** I acknowledge that inclusion of Moxidectin in the WHO EML/EMLc is an essential step to enabling both sustainable access and implementation in endemic countries as an alternative tool for the treatment or prevention of onchocerciasis and lymphatic filariasis. **However, at this time I cannot recommend including Moxidectin to WHO EML/EMLc based on the following considerations: (1) Moxidectin is not wildly available on the market**, which was only approved by the US FDA for the treatment of onchocerciasis due to O. volvulus in patients aged 12 years and older. **(2) The price for Moxidectin in endemic countries outside the US is uncertain.** Although modelling suggests that the overall programmatic costs for Moxidectin-based MDA over the reduced time period could be saving compared with current Ivermectin strategy, the precondition is that the production capacity reaches 1.9 million treatments per year and the proposed price for Moxidectin per 8 mg dose (4 x 2 mg tablets) is US$1.56. **The cost-effectiveness evaluation should be based on the real-world study if Moxidectin is used as a preferred regimen over Ivermectin. (3)** So far, the safety of single dose Moxidectin compared to single dose Ivermectin is under assessment in participants 4 years and older**. The FDA label for Moxidectin use in children 4-11 years has not approved, thus, we can recommend Moxidectin for inclusion in the EMLs currently.**

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

Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**)	☒ Yes ☐ No ☐ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (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
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (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;) For children 4-11 years, the safety profile data have not published.	☐ 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? (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? (e.g. shortages, generics and biosimilars, pooled procurement programmes, access programmes)	☐ Yes ☒ No ☐ Not applicable
Does the medicine have wide regulatory approval? Just approved for use in the US.	☐ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☒ No ☐ Not applicable