Moxidectin for Onchocerciasis

Frequently Asked Questions

Background

The World Health Organisation (WHO) Roadmap for Neglected Tropical Diseases 2021 to 2030 includes a critical action to identify more effective treatments for onchocerciasis. A specific recommendation is made to *"demonstrate effectiveness and safety of moxidectin in children and in programmatic settings (could replace the need for semiannual ivermectin MDA)"*.

In December 2021, the 5th meeting of the Onchocerciasis Technical Advisory Subgroup (OTS) of the WHO endorsed the use of moxidectin for onchocerciasis in pilot field projects. During 2022, Medicines Development for Global Health began working with partners to plan for these field projects. Medicines Development sought further advice of the OTS at its 6th meeting in December 2022 for a proposed process for selecting suitable locations for implementation of the pilot projects. The outcome of these pilot projects will be to support the broader use of moxidectin as an alternative treatment strategy for consideration by National Onchocerciasis Elimination Programmes and in particular, for areas with ongoing elimination challenges. During 2023 Medicines Development for Global Health will share more information about the pilot field projects and hold discussions with interested countries with a potentially suitable location to undertake such a project.

In recent discussions with countries seeking to eliminate transmission of onchocerciasis and their partners, questions have been raised about moxidectin. This document provides a summary answer to some of the most common questions posed.

Moxidectin Background

Medicines Development for Global Health, in collaboration with the UNICEF/UNDP/World Bank/WHO Special Programme for Research in Tropical Diseases (WHO TDR), completed a core program of clinical trials and received regulatory approval from the United States Food and Drugs Administration (US FDA) in 2018 for moxidectin for the treatment of onchocerciasis in people aged 12 years and older.[1]
Recently, Medicines Development completed a study in children and adolescents. The data from this study was used to select a dose of moxidectin for treatment of children 4 to 11 years for onchocerciasis for further study.

Currently, Medicines Development is sponsoring further clinical trials to support implementation of moxidectin in community treatment programmes. These clinical trials will provide data to:

1) further characterise the safety of moxidectin s (underway in the Democratic Republic of Congo (DRC) and Cote D'Ivoire), and
2) compare the efficacy and safety of repeated annual and biannual treatments with moxidectin or ivermectin (DRC).

Medicines Development for Global Health background

Medicines Development for Global Health is an independent, non-profit biopharmaceutical company dedicated to the development of medicines for those who need them most. The company is funded through grants, philanthropy, and social impact investment to further develop its medicines. This funding is used to support ongoing clinical trials, manufacturing of moxidectin tablets and the many development activities needed to support the transition of moxidectin into programmatic use for onchocerciasis.

Medicines Development for Global Health is the marketing authorisation holder and manufacturer of moxidectin tablets for human use. The company is working towards making moxidectin available for community-directed treatment, exploring partnerships and joining in ongoing efforts to find solutions for sustainable financing and supply of medicines for Neglected Tropical Diseases (NTDs).

Medicines Development for Global Health

Moxidectin for Onchocerciasis

Frequently Asked Questions

Frequently Asked Questions (FAQs)

1. **Is moxidectin approved for use in people?**
   Moxidectin has been approved by the US FDA for treatment of onchocerciasis in patients aged 12 years and older. The US FDA is a stringent regulatory authority. US FDA approval may be considered by other National Regulatory Authorities to support country registration of moxidectin.

2. **How do I find information about moxidectin?**
   In addition to the multiple publications, the US FDA prepares and publishes the "Prescribing Information" which provides a summary of scientific data about moxidectin relevant to the approved use https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210867s003lbl.pdf Information including the approved indication, risks and precautions, safety data, drug:drug interaction risks, pregnancy and breast-feeding advice are included in this document.[1]

3. **Has Medicines Development for Global Health applied for endorsement of moxidectin for community use by the World Health Organisation (WHO)?**
   Medicines Development for Global Health has been working with the WHO to provide the information needed to endorse the use of moxidectin in onchocerciasis elimination programmes. The WHO NTD Roadmap, published in January 2021, recommends that moxidectin be assessed in programmatic settings. As a result, Medicines Development for Global Health has started to engage with countries to run pilot field projects with moxidectin.

4. **Is moxidectin on the WHO prequalified list?**
   Moxidectin has been approved by the US FDA, a stringent regulatory authority which allows for its consideration, like that of ivermectin, for use without prequalification. However, Medicines Development for Global Health intends to work with the WHO to support the necessary steps to achieve national registrations and inclusion in the list of WHO prequalified medicines.

5. **Is moxidectin on the WHO Essential Medicines list?**
   No. Once the WHO Guideline Development process is underway, Medicines Development for Global Health plans to apply for the addition of moxidectin to the WHO Essential Medicines List.

6. **Is moxidectin the same as ivermectin**
   Moxidectin and ivermectin are from the same family of medicines called macrocyclic lactones, but they have some important structural differences. Moxidectin is more lipophilic (attracted to fatty tissue) than ivermectin which means it is retained in the body and is effective for much longer. Also, unlike ivermectin, moxidectin is minimally metabolised by the body, which means it does not affect the pharmacokinetics of other drugs.

7. **Is moxidectin a microfilaricide?**
   Like ivermectin, moxidectin has a microfilaricidal effect as it damages the microfilariae resulting in their death by the immune response of the infected person. In addition, moxidectin affects the ability of the adult worm to produce new microfilariae, resulting in a long-term reduction of microfilariae in the skin.

8. **How long does this effect last?**

   For people who have received moxidectin in clinical trials, the suppression of microfilariae lasts at least 6 months, and some people had no microfilariae in their skin up to 18 months after treatment. Moxidectin is not curative with a single treatment, but data on repeated treatments with long follow-up times are currently being generated to evaluate this.[2]

9. Is moxidectin a macrofilaricide?

No. Moxidectin does not kill adult *O.volvulus* worms. There is currently no data showing whether moxidectin has any permanent effects on the adult worms, including permanent sterilization, but the outcome of the repeat-dose study (MDGH-MOX 3001) will provide further information on the impact of moxidectin on adult worms.

10. How does moxidectin work?

Like ivermectin, moxidectin binds to targets in the parasite necessary for muscle and nerve function. This binding results in disrupting parasite functions such as feeding, reproduction, and the ability of microfilariae to evade the host immune system.

11. How does efficacy of moxidectin compare to ivermectin?

Compared to ivermectin, a single dose of moxidectin:

- results in undetectable levels of onchocerciasis skin microfilariae in at least 8 times more infected people at 6 months (92% vs 11%) and 12 months (46% vs 5 %) after treatment (*Opoku et al 2018*);
- generates a consistent treatment response across the whole population for at least 6 months;
- remains in the skin longer, keeping microfilariae at very low levels and decreasing the risk of transmission between treatments.

A randomized, ivermectin control, double-blind Phase 3 study conducted in Ghana, Liberia, and the DRC showed that among people infected with *O. volvulus* and treated with moxidectin, 91.5% had undetectable levels of microfilariae at 6 months and 45.9% at 12 months compared to 11.5% and 5.4% in people treated with ivermectin.[3] Even at 18 months after treatment, the percentage of participants with undetectable skin microfilariae was significantly greater in those treated with moxidectin compared with ivermectin.

Moreover, a consistent microfilaricidal response was shown in those receiving moxidectin compared with those treated with ivermectin in whom a high degree of inter-individual variability in microfilariae responses was shown. This variability with ivermectin treatment, previously described as 'sub-optimal response', was not seen with moxidectin treatment in the Phase 3 trial.

Moxidectin has a plasma half-life of 23.3 days in people infected with *O volvulus*,[1] compared with less than 1 day (18 hours) for ivermectin.[4] This translates into ongoing presence of drug and much longer suppression of skin microfilariae, reducing the potential for transmission from person to person by biting black flies.
This suggests that the use of moxidectin in treatment of endemic communities may more effectively block and eventually interrupt onchocerciasis transmission.

12. How does moxidectin's safety compare to ivermectin?

As a summary, the comparative safety profile of moxidectin is

- similar to placebo, in healthy volunteer studies, at doses up to 36mg, 4.5x the dose used for onchocerciasis
- similar to ivermectin, in Phase 2 and 3 clinical trials in onchocerciasis- infected individuals, in terms of type, severity and duration of events.

In healthy volunteer studies, the adverse event profile of moxidectin was similar to placebo at doses up to 36 mg, or 4.5 times the dose used for onchocerciasis.
In the Phase 2 and 3 clinical trials in onchocerciasis infected individuals, the safety profile of moxidectin was similar to ivermectin in terms of type, severity and duration of events.[3,5] As with ivermectin, commonly reported adverse events were associated with a host immune response to the dead and dying *O. volvulus* microfilariae**. There was a small increase in the proportion of

people experiencing these events with moxidectin, reflecting its greater efficacy. Importantly, the severity of these events was not different than with ivermectin treatment. No serious adverse events reported in the clinical trials were assessed as related to either moxidectin or ivermectin treatment. No differences were observed in the safety profile for moxidectin across all ages and both sexes.

** Moxidectin use is associated with an immunologically mediated reaction to the death of microfilariae known as the Mazzotti reaction, characterised by pruritus, headache, pyrexia, rash, urticaria, hypotension (including symptomatic orthostatic hypotension and dizziness), tachycardia, oedema, lymphadenopathy, arthralgia, myalgia, chills, paresthesia and asthenia. Ophthalmological manifestations include conjunctivitis, eye pain, eye pruritus, eyelid swelling, blurred vision, photophobia, changes in visual acuity, hyperaemia, ocular discomfort and watery eyes. These adverse reactions generally occur and resolve in the first week post-treatment and do not require medical intervention. The clinical studies have shown that moxidectin is well tolerated and similar to ivermectin suggesting that it is compatible with community-directed treatment.

13. Are there any contraindications/ precautions for use of moxidectin?

There are no contraindications for the use of moxidectin in onchocerciasis patients specified in the current United States Prescribing Information.[1]

a) There is no need for dose adjustment in elderly patients, patients with impaired kidney function or impaired liver function.
b) While there are no contraindications identified for moxidectin, there are insufficient data on the use of moxidectin in pregnant women to establish whether there is a moxidectin-associated risk for major birth defects and miscarriage. Avoidance of use in pregnancy is advised unless the benefit to the mother outweighs any potential risk to the unborn child.
c) Breastfeeding is not recommended at the time of treatment with moxidectin and for 7 days after treatment.

However, precaution is advised in the following circumstances:

- Co-infection with *loa loa*. Specific information on safety in *L. loa* is yet to be generated in clinical studies. Screening of individuals exposed to *L.loa* is advised before using moxidectin to treat onchocerciasis. Until further data is available, moxidectin use in treatment programmes in areas co-endemic for *L.loa* is not advised.
- People with hyper-reactive onchodermatitis (sowda) may be more likely than others to experience severe oedema and worsening of onchodermatitis

14. Can moxidectin be given with other NTD drugs?

There are no known drug:drug interactions between moxidectin and other drugs.

Moxidectin has a low likelihood for drug:drug interactions based on its absorption, distribution, metabolism and excretion profile. In healthy subjects, co-administration of a single 8 mg oral dose of moxidectin tablets did not have an effect on the pharmacokinetics of midazolam, well known to interact with other drugs. Moxidectin can be co-administered with drugs that are CYP3A4 metabolic enzyme substrates.

a) Moxidectin has been used together with albendazole in trials against gastrointestinal nematodes (including *Trichuris*). No differences in safety (adverse events) have been reported for the combination compared with either drug alone in these studies.[6,7]
b) The effect of moxidectin or ivermectin in combination with albendazole with or without diethylcarbamazine (DEC) has been studied in a clinical study of bancroftian lymphatic filariasis (LF) in Cote D'Ivoire. This study included an assessment of drug:drug interaction potential in an initial group of participants before proceeding to full enrolment of the study (results pending). Results presented to date (ASTMH 2021) indicate that using moxidectin, albendazole +/- DEC together did not adversely affect safety compared with ivermectin

combinations.[8]
For more information, please refer to the Prescribing Information.[1]

15. Can moxidectin be given to pregnant women?

In common with most medicines, there are limited data on the use of moxidectin in pregnancy. As for the similar drug, ivermectin, it is not recommended for use in pregnant women.
For more information, please refer to the Prescribing Information.[1]

16. When will the paediatric dosing of moxidectin be complete so it can be used in programmes?

Based on the current US approved indication, moxidectin is recommended for treatment of onchocerciasis in people aged 12 years and older. Using data from the paediatric clinical trial in Ghana (publication of the full study results expected in 2023) a dose was successfully identified for treatment of children 4 to 11 years. While the data from this study will support an application to the USFDA for inclusion of children down to 4 years, MDGH plans to start enrolling children aged 4 to 11 years in an ongoing safety study in DRC and Ivory Coast from May 2023.

17. Is moxidectin available now? How can we access it?

Currently, moxidectin for use in onchocerciasis endemic communities is only available through participation in pilot field projects or clinical trials.

For more information on how to request moxidectin for clinical trials use or how your country could participate in a pilot field project, please contact Medicines Development for Global Health at MoxidectinPilot@medicinesdevelopment.com

18. Is moxidectin donated?

For selected pilot field projects moxidectin tablets will be donated.
Sustainable options for the ongoing supply of moxidectin for wider field programmes are being investigated.

19. How will moxidectin be supplied for pilot field projects?

Moxidectin will be supplied in white bottles of 500 tablets with a Prescribing Information leaflet attached to the bottle. Moxidectin 2 mg tablets are white to pale yellow in colour, uncoated and oval shaped. The shelf-life is currently 2-years from date of manufacture. Medicines Development for Global Health is generating additional data to support future extension of the shelf-life. The bottles should be stored below 30°C.

For more information, visit Medicines Development for Global Health's website:
https://www.medicinesdevelopment.com.

References

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