

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, at the 5th meeting of the Onchocerciasis Technical Advisory Subgroup (OTS) of the WHO endorsed the use of moxidectin for onchocerciasis for pilot field projects. During 2022, Medicines Development for Global Health began working with partners to plan for these field projects. Currently, there is interest in the use of moxidectin in areas that present an ongoing challenge for National Onchocerciasis Elimination Programmes, including where no community-directed treatment (CDT) efforts have yet been employed or where special circumstances have resulted in ongoing CDT efforts not yet achieving elimination goals. Special circumstances include but are not limited to zones with migratory populations, cross-border onchocerciasis transmission zones, and/or persistent hot spots of transmission.

In recent discussions with countries seeking to eliminate transmission of onchocerciasis, where the introduction of moxidectin is being considered, several questions have been raised. This document provides a summary answer to 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 the 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

Medicines Development for Global Health is sponsoring further clinical trials to support implementation of moxidectin in community-directed treatment (CDT) programmes. These clinical trials will provide data to:

- 1) further characterise the safety of moxidectin compared with ivermectin to support the use of moxidectin for CDT (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).
- 3) select a dose of moxidectin for children 4 to 11 years to treat onchocerciasis. It is anticipated that children in this age group will then be included in clinical studies and pilot field projects, subject to regulatory and ethics approvals.

Medicines Development for Global Health background

Medicines Development for Global Health is an independent non-profit 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, among other activities, ongoing clinical trials, manufacturing of moxidectin tablets and the many tasks 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

mass drug administration, exploring partnerships and joining in ongoing efforts to find solutions for sustainable financing and supply of medicines for Neglected Tropical Diseases (NTDs).

Frequently Asked Questions (FAQs)

1. Is moxidectin approved for use in people?

Moxidectin has been approved by the US FDA for treatment of onchocerciasis patients 12 years and older. The US FDA is a stringent regulatory authority, and approval by them represents the highest standard of pharmaceutical review.

2. How do I find information about moxidectin?

The US FDA prepares and publishes the “Prescribing Information” which provides a physician’s summary of all the known data about moxidectin. Information including the approved indication, risks and precautions, safety data, drug:drug interaction risks, pregnancy and breast feeding advice are included in this critical document.¹

3. Is moxidectin endorsed for community directed treatment by the WHO?

Moxidectin has not yet received endorsement by the WHO for community directed treatment of onchocerciasis.

4. Has Medicines Development for Global Health applied for endorsement for community use by the WHO?

Medicines Development for Global Health has been working with the WHO to provide it with the information it needs to make a recommendation on moxidectin. The WHO NTD Roadmap, published in January 2021, recommends that moxidectin be assessed in programmatic settings and Medicines Development for Global Health is collaborating with the WHO to take the necessary steps in this next stage for moxidectin. During the 5th meeting of the WHO OTS held in December 2021, the programmatic use of moxidectin in pilot field projects was endorsed. It is anticipated that moxidectin field projects will be discussed again at a 6th meeting of the WHO OTS (Dec 2022) and further advice for implementation of pilot projects provided.

5. Is moxidectin on the WHO prequalified list?

The prequalification process is generally to provide quality reassurance of manufacture for products outside of a stringent regulatory authority approval. Currently moxidectin is not on the WHO’s prequalification list but it is approved by the US FDA, a Stringent Regulatory Authority (SRA). This provides the highest level of quality assurance of moxidectin tablets.

6. Is moxidectin on the WHO Essential Medicines list?

No. Medicines Development for Global Health is preparing an application for the addition of moxidectin to the 2023 WHO Essential Medicines List.

7. 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. Also, unlike ivermectin, moxidectin is minimally metabolised by the body.

Although at least 6 medicines from this family are approved for veterinary use, only moxidectin and ivermectin are also approved for use in humans.

8. How does moxidectin work?

Moxidectin (and ivermectin) targets a parasite-specific target called glutamate gated chloride channels, essential for parasite muscle function. Humans do not have this target. Both moxidectin and ivermectin also have activity against a target called GABA found in parasites and humans. These effects result in a compromise to parasite function, including feeding, reproduction, and ability to hide from the host immune system.

9. Is moxidectin a macrofilaricide?

There is no data that supports moxidectin acting as a macrofilaricide.

10. Is moxidectin a microfilaricide?

Neither moxidectin nor ivermectin directly kill *Onchocerca volvulus* microfilariae. Both treatments compromise 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.

11. How long does this effect last?

For all people who have received moxidectin in clinical trials, this effect lasts at least 6 months and, in some people, they have no microfilariae in their skin 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

12. How does efficacy moxidectin compare to ivermectin?

A single dose of moxidectin significantly decreases skin microfilariae densities in more infected people, to lower levels and for much longer than ivermectin.

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, over 92% 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 eliminate onchocerciasis transmission.

13. How does moxidectin’s safety compare to ivermectin?

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. There was no effect on blood parameters

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 reflects its greater efficacy. However, 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 and including 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.

14. 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 (March 2021) United States Prescribing Information.¹

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
- 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.

15. Can moxidectin be given with other NTD drugs?

There are no known drug:drug interactions, and moxidectin has a low likelihood for drug:drug interactions based on its absorption, distribution, metabolism and excretion profile. In healthy subjects,

concomitant administration of a single 8 mg oral dose of moxidectin tablets did not have an effect on the pharmacokinetics of midazolam. Moxidectin can be co-administered with CYP3A4 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. Results to date indicate that using moxidectin, albendazole and DEC together did not adversely affect the pharmacokinetics of these medicines. In addition, safety of the moxidectin combinations has been reported as similar to ivermectin combinations.⁸

For more information, please refer to the Prescribing Information.¹

16. 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.

17. 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. A paediatric clinical trial to support selection of a dose for treatment of children 4 to 11 years is currently concluding. Reporting of data from this study is anticipated in late 2022.

18. 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

19. 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.

20. How will moxidectin be supplied?

Moxidectin will be supplied in white high-density polyethylene (HDPE) 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. Once opened, the contents of the bottle should be used within 24 hours.

References

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