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Statement on miltefosine – Geneva 20 03 2023

Advisory Committee on Safety of Medicinal Products (ACSoMP): Measures to minimize the risk of ocular adverse events with miltefosine

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP), supports the recommendations of the WHO ad-hoc Multidisciplinary Technical Group (MTG) which was set up to investigate a signal of ocular adverse events following the use of miltefosine, and provides the following advice to minimize the risks of ocular adverse events in patients exposed to miltefosine:

Information for patients

- Before starting the treatment containing miltefosine, tell your healthcare professional if you currently have any eye problem or history of eye problem as an ocular examination should be done first in these situations
- If you experience any eye discomfort during the treatment, discontinue miltefosine immediately and contact your nearest healthcare centre or a healthcare professional as soon as possible
- Please contact your nearest healthcare professional if you have any question or concern.

Information for healthcare professionals

- Before starting the miltefosine treatment the history of eye disorders should be collected and an eye examination should be done as appropriate.
- In case of current or past history of ocular disorder, the benefits and the risks of treating a patient with miltefosine should be carefully considered, and advice from an ophthalmologist should be sought where feasible.
- All patients should be informed before starting the treatment that in case of eye problems during the treatment (e.g. red eyes, increased watering, eye pain, blurred vision) they should discontinue miltefosine and contact their healthcare professional immediately.
- If ocular complications occur and a connection with miltefosine cannot be excluded, miltefosine should be discontinued immediately and an alternative treatment for leishmaniasis should be initiated if necessary. Since miltefosine has a very long half-life (>6 days), it is possible that ocular changes will not be reversible without treatment even after discontinuation of miltefosine. Therefore, an eye specialist should be consulted in such cases to avoid the possibility of permanent damage.
- Please refer to the Guiding principles, provided below, for prevention, early detection and management of eye complications in patients treated with miltefosine, for further information.
- Suspected adverse events should be reported to local health authorities and the national pharmacovigilance programme without delay.

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Background information

Miltefosine is an oral anti-infective and one of the medicines with established efficacy in the treatment of some forms of leishmaniasis, a parasitic infection spread by the bite of infected female phlebotomine sandflies. Leishmaniasis can take different clinical forms, including cutaneous leishmaniasis, mucocutaneous leishmaniasis, and visceral leishmaniasis (VL).

Post-Kala-Azar Dermal Leishmaniasis (PKDL) is a sequela which can generally occur 6 months to several years after apparent cure of VL. Although uncommon, leishmanial ocular manifestations have been reported, and keratitis and uveitis can also occur with the disease. A 12-week treatment course of Miltefosine is used to treat PKDL specific to VL endemic countries in South-East Asia.

Following reports of ocular disorders following miltefosine use originating mostly from South-Asia, ACSoMP had recommended WHO to further investigate this issue[1]. The proposed method was discussed with ACSoMP in June 2022 and WHO established an ad-hoc Multidisciplinary Technical Group (MTG) to advise on the causality, the risk characteristics and frequency, risk minimization measures, risk communication, remaining uncertainties and the need for further studies.

To facilitate the work from the MTG, the WHO, supported by the German National Regulatory Authority (BfArM) and the Uppsala Monitoring Centre (UMC), collected and compiled all available evidence and information on the causal relationship between reports of serious ocular events and exposure to miltefosine.

Based on the available data, the MTG considered that a causal relationship between ocular adverse events and the exposure to miltefosine is at least a reasonable possibility. The risk of ocular adverse events, such as redness of the eye, inflammation of different eye structures (keratitis, scleritis, uveitis) and visual impairment up to blindness has been observed mostly during the treatment of patients with PKDL in South Asia in both men and women, including in children under 18-year-old, and mostly beyond 28 days of treatment. No further risk factor could be identified. When the information was available, most of the cases resolved after miltefosine was withdrawn, sometimes after a symptomatic treatment was started. However, in some cases, the adverse ocular event led to permanent loss of sight. The frequency of adverse ocular events during treatment with miltefosine could not be estimated based on the available data, and the mechanism of action remains unclear.

The ACSoMP discussed during its meeting on 14 December 2022 the issue of ocular adverse events with miltefosine and advised the following (https://www.who.int/publications/m/item/2022-december-acsomp-recommendations):

[1] WHO. Statement on miltefosine - Potential ocular disorders in patients treated with miltefosine for post-kala-azar dermal leishmaniasis (PKDL). 10 February 2022. URL: https://www.who.int/news/item/10-02-2022-statement-on-miltefosine---potential-ocular-disorders-in-patients-treated-with-miltefosine-for-post-kala-azar-dermal-leishmaniasis-(pkdl)#:~:text=Miltefosine%20is%20an%20oral%20anti,and%20visceral%20leishmaniasis%20(VL).

- the inclusion of the proposed warning and list of ocular adverse events in the summary of product characteristics and the patient information leaflet for miltefosine. All stakeholders should ensure that product information is provided in a language that is understood by local healthcare professionals and patients to enable effective risk communication;
- the additional guiding principles for the prevention, early detection and management of eye complications in patients treated with miltefosine;
- the development of a patient information brochure by WHO based on the MTG recommendations to facilitate risk communication;
- communication via a statement on WHO's website, the publication of the public assessment report and publications in peer-reviewed journals
- communication of conclusions through disease programmes and to investigators of identified ongoing clinical trials;
- in countries where it is feasible, a Direct Healthcare Professional Communication by national regulatory authorities;
- the use of active surveillance (such as a cohort event monitoring (CEM) study), supported by a follow-up questionnaire, to characterize the risk and its frequency and to assess the effectiveness of the risk minimization measure;
- Collaboration of PV programme with disease progamme, to ensure efficient real time data sharing, rapid analysis and interpretation;
- implement a study analysing miltefosine pharmacokinetics, the presence of parasites and immune reactions in patients with PKDL to assess the specificity and causality of this adverse event in these patients.

As a precautionary measure, and although the risk appears to be mostly reported in patients with PKDL in South-Asia, the above recommendations and advisories should also be considered in other patients exposed to miltefosine.

Further details are provided in annex attached, including:

- Wording recommendations for product information
- Guiding principles for prevention, early detection and management of eye complications in patients treated with miltefosine
- A follow-up questionnaire for incorporation into active surveillance projects.

Contact: pvsupport@who.int

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Annex 1 - Recommended wording in the SmPC and PIL

The following wording were recommended by the MTG, based on those pre-existing in the product information which was shared by the manufacturer/Marketing authorization holders of the originator product (the changes are underlined):

Summary of Product Characteristics

Section 4.4 Special warnings and precautions for use

Ocular changes ~~such as keratitis~~ are well-known symptoms of leishmaniasis. However, in ~~a few~~ case reports mainly from South Asia, predominantly ~~particularly~~ in the treatment of post-kala-azar dermal leishmaniasis (PKDL), ocular complications such as unilateral or bilateral keratitis and visual impairment, sometimes permanent, occurred after miltefosine had been administered for a few days or several weeks. In most of these cases, miltefosine had been administered for PKDL during 12 weeks, longer than the recommended therapy duration of 28 days in the treatment of VL. In published case reports, patients who developed ocular complications under miltefosine and who were therefore treated with topical glucocorticoids showed an improvement of symptoms 1;2;3. Before starting the treatment eyes examination should be considered and the history of ocular disorders should be collected. In case of current or past history of ocular disorder, the benefits and the risks of treating a patient with miltefosine should be carefully considered, and advice from an ophthalmologist should be sought if feasible. All patients should be informed before starting the treatment that in case of eye problems (e.g. red eyes, eye pain, blurred vision) they should discontinue miltefosine and contact their healthcare professional immediately. If ocular complications occur and a connection with miltefosine cannot be excluded, miltefosine should be discontinued immediately and an alternative treatment for leishmaniasis should be initiated if necessary. Since miltefosine has a very long half-life, it is possible that ocular changes will not heal without treatment even after discontinuation of miltefosine. Therefore, an eye specialist should be consulted in such cases to avoid possible permanent damage. See also Sections 4.8 and 4.9 [of the SPC].

1) https://dx.doi.org/10.1136/bjophthalmol-2020-317325

2) https://doi.org/10.1371/journal.pntd.0006781

3) https://doi.org/10.1177/0049475520929822

Section 4.8 of the SmPC:

SOC eye disorders* under the frequency category “Not known” (cannot be estimated from the available data): keratitis, keratopathy and acute scleritis, uveitis, ocular hyperaemia (increased ocular vascularity) and visual impairment up to blindness

*most cases have been reported for treatment of PKDL, see also section 4.4

Patient information leaflet

2. What should you know before taking <product name>?

Eye problems, such as inflammation of the cornea (keratitis), can be symptoms of the Leishmania infection. ~~In a few cases,~~ However, in some cases, eye problems up to blindness, sometimes permanent, occurred after taking <product name> for a few days or several weeks. Before starting the treatment, tell your healthcare professional if you have any eye problem or history of eye problem as an ophthalmological examination should be done first. If you experience any eye discomfort during the treatment, discontinue miltefosine immediately and contact your doctor ~~immediately~~ as soon as possible ~~Contact your doctor immediately if you notice any eye problems~~ (see also below under "Side effects").

4. What are the possible side effects?

Cases of eye complaints such as ~~corneal inflammation (keratitis), corneal disease (keratopathy) or inflammation of the sclera (acute scleritis) were~~ redness of the eye and inflammation of different eye segments (keratitis, scleritis, uveitis) and visual impairment up to blindness have been reported after taking <product name> ~~for several weeks~~ (exact frequency of occurrence cannot be estimated). Discontinue the treatment immediately and contact your doctor/next clinic ~~immediately~~ as soon as possible if you notice any eye complaints including ~~as~~ foreign body sensation, redness, pain, sensitivity to light, blurred vision or corneal opacity. ~~Contact your doctor immediately if you notice any eye problems such as a foreign body sensation, redness, pain, sensitivity to light, blurred vision, or corneal opacity.~~

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Annex 2 Guiding principles for prevention, early detection and management of eye complications in patients treated with miltefosine

Guiding principles for prevention, early detection and management of eye complications

The guiding principles proposed in this document require careful adaptation to the local context.

Roles, lines of communication and pathways of referral for health personnel should be clearly defined to effectively detect, prevent, and manage eye complications in patients treated with miltefosine.

In general, health personnel (e.g., physicians, dermatologists, pharmacists, disease programme officers, ophthalmologists, and any other relevant healthcare professionals and health workers) dealing with leishmaniasis or other conditions where miltefosine is prescribed should be aware of the risk of eye complications during or following treatment with Miltefosine.

The Ophthalmologists practicing in the areas where Leishmaniasis is prevalent should be connected to some tertiary centres when required. In places where ophthalmologists are not available General doctors should be referred to an eye specialist. Collaborations with the national blindness prevention and control programmes should be considered as required.

When starting a treatment with miltefosine

a. Confirm the condition/diagnosis which requires administration of miltefosine (in certain settings, experts agree that probable diagnosis is sufficient to prescribe miltefosine, e.g., post-kala-azar dermal leishmaniasis (PKDL) in the elimination context of South-Asia)
b. Confirm if the patient was previously treated with miltefosine and, if so, whether any adverse event occurred.
c. Contact details of the patients should be collected to allow for follow-up
d. Patients should be explained about the diagnosis, treatment choices, duration of treatment and possible side effects of prescribed drug(s)
e. Patient should be explained about the frequent follow-ups and should be provided with a patient information brochure, if available.
f. Pre-Prescription eye check-up for any concomitant eye conditions (please see below checklist). If any issue was identified:
    i. In patients with severe ocular disorders (especially keratitis, uveitis, scleritis), initiation of miltefosine should be deferred till the complete resolution of lesions. An ophthalmology consultation may be required for the diagnosis and management.

ii. If the patient has a history of recurrent episodes of ocular redness and/or pain and any known immune disorder affecting the eyes, a review of all old records and proper eye examination with the investigation is recommended prior to initiation of miltefosine.
iii. If the patient has a history of ocular changes during miltefosine treatment for VL or previous PKDL, there should be an interval of at least 4 weeks before initiation of miltefosine (keeping a half-life of the drug of 31 days). These patients should be under more frequent follow-ups, preferably every fortnight.

g. Patients and their family members should be counselled about the possible risks and adverse events of the prescribed drug(s).
h. Importantly, they should be advised to immediately stop the treatment by miltefosine and report to the nearest health centre or health worker if any ocular symptoms are noticed. Especially, one or several of the following symptoms may occur in a single or both eyes and require immediate attention:
    i. Redness
    ii. Irritation in the eye
    iii. Watering
    iv. Pain
    v. Photophobia (unable to tolerate light)
    vi. Loss/Dimness of eyesight
    vii. Cloudy appearance of the eye
    viii. White spots in the eye
i. All patients on miltefosine should be followed-up at frequent interval during the treatment and a minimum of up to 2 months after the treatment. An eye examination at completion of 4 week therapy is of critical importance.

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Pre-prescription eye check-up (all information may not be available)

Is there any current diagnosed/undiagnosed eye problem?

1) If yes, what kind of eye problem?
   i) Redness
   ii) Pain
   iii) Irritation
   iv) Watering
   v) Discharge
   vi) Photophobia (intolerance to light)
   vii) Low vision. If available,
      (1) visual acuity:
      (2) colour vision:
   viii) Cloudy appearance of the eye
   ix) White spots in the eye
   x) Corneal infiltration
   xi) Corneal ulceration
   xii) Abnormality of eye lid or eyelashes:
   xiii) Any other symptom (please specify):
2) In which eye? Right Left Both
3) How long has the eye problem been happening?
4) Any Ophthalmic consultation?
   a) If so, diagnosis by ophthalmologist:
5) Any treatment for the eye problem?
6) Medications prescribed for eye problem
7) Name and place of eye treatment facility:
8) Have the symptoms:
   Persisted/ resolved / deteriorated ?

If an eye adverse event occurs

Patients should be immediately referred to a healthcare professional and treatment by miltefosine should be stopped.

Patients/health personnel: The adverse event should be reported to local health authorities and the pharmacovigilance programme. Any ocular adverse event should be reported to WHO by national authorities for further analysis and guidance.

When feasible,

a. The patient should be referred and/or brought to the nearest higher health facility where eye care facilities or ophthalmology services exist and/or referred to an ophthalmologist. Tele-consultation with an ophthalmologist may also be considered.
b. Eye specialists are invited to consider the following:
    i. Any anterior segment inflammation like Episcleritis, Scleritis, limbal nodules, Keratitis, especially peripheral corneal infiltrations should be looked at with suspicion. Meticulous history should be taken to know about any trauma and concomitant medication during leishmaniasis treatment.
    ii. A corneal smear or appropriate microbiological sample may be taken if facilities exist and if deemed necessary by the treating ophthalmologist. However, treatment should not be delayed irrespective of sample availability.
c. If there is a history of Miltefosine intake and common eye infections are ruled out,
    I. Features of inflammation of eye structures like sclera, cornea etc, may be managed by topical steroid and antibiotic, as required, along with other symptomatic management such as cycloplegic drops and artificial tears, depending upon the severity and other concomitant or super added infections.
    II. If symptoms involve both the eyes, then associated underlying systemic disease conditions (e.g., diabetes mellitus, immunosuppressive disorders) should be ruled out.
    III. All patients not responding to above or due to worsening in one week therapy should be referred to higher centres, with facilities of ophthalmic consultation and compliance with the treatment of the ocular adverse event(s) should be checked.
    IV. Patients of extreme age (paediatric or elderly age) should be under close observation or referred to higher centres. with facilities of ophthalmic consultation
    V. Detection or refractory errors and other eye conditions like cataract, glaucoma should be managed in coordination with the national blindness prevention and control programme.

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Annex 3 Follow up Questionnaire

When a report of ocular event in a patient treated with miltefosine is received using a standard reporting form, this follow-up questionnaire is intended for the disease and/or pharmacovigilance programme to systematically collect key available information. It is not intended for front-line staff.

The objectives of this follow up questionnaire are:

1) to better characterise the risk, especially risk factors and occurrence in other clinical forms than PKDL,
2) to assess the effectiveness of the recommended risk minimisation measures.

The collected information should be shared with both the disease and the pharmacovigilance programme without delay. Any ocular adverse event should be reported to WHO by national authorities for further analysis and guidance.
The information already provided in the previous report(s) should not be asked again to the reporter. To address unknown information, the questionnaire may be administered through any convenient means (including face to face, telephone, email, etc.). Several follow up may be conducted if important information is awaited. Reasonable attempt should be made to contact the reporter again if no response is received.

A: Information about the patient and the reporter

A. 1. Information about the patient (information at the time of the suspected drug consumption)

Initials/Name: **Other patient ID:**	**Sex:** □ Male □ Female □ Other *If pregnant. Trimester:* I II III *OR date of last menstrual period:* _ _ / _ _ / _ _ _ _ *Breast-feeding?* □Yes □ No **Patient Weight** *(kg/other units)* _____ *(if available)* **Patient Height** *(cm/other units)* _____ *(if available)*	**Date of Birth:** _ _ /_ _ / _ _ _ _ **OR Age:** **_ _ Years _ _ Months _ _ _ Days** **OR Patient age group (if exact age not known):** **□ 0 < 1 year □ 1- 5 years □ > 5 years - 18 years** **□ > 18 years – 60 years □ > 60 years**

A. 2. Information about the reporter

□ Physician, □ Pharmacist, □ Other Health Professional, □ Lawyer, □ Consumer □ Other non-health professional (specify):	
Reporter's Name (given and family names):	**Designation:**
Address: Locality, District, Province	
E-mail address:	**Telephone:**

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B. Suspect and concomitant Drug(s), and any other information

B. 1. Miltefosine	
Brand name of drug	
Daily dose(s)	
Indication for use, type of leishmaniasis	
Date treatment was started	
Date treatment was stopped	
Outcome of the suspected reaction after stopping the treatment: Symptoms: ● ● ●	Date of control: Outcome: Persisted / resolved / deteriorated Outcome: Persisted / resolved / deteriorated Outcome: Persisted / resolved / deteriorated
Was the treatment re-started?	Yes / No
If treatment was re-started: Date treatment with miltefosine was started: Any ocular event after restart? If Yes, please provide details: Date treatment was ended/discontinued: Outcome of the symptoms after discontinuation: Symptoms: ● ● ●	 Yes / No Date of control of symptoms outcome: Outcome: Persisted / resolved / deteriorated Outcome: Persisted / resolved / deteriorated Outcome: Persisted / resolved / deteriorated

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B.2. Any other suspected and concomitant drugs, including traditional medicines:

Product Name and Drug form (tablet etc.)	Dose/ Unit	Manufacturer	Batch/lot number	Route of admin.	Indication	Treatment started	Treatment stopped
Suspected drugs							
						__/__/____	__/__/____
						__/__/____	__/__/____
						__/__/____	__/__/____
						__/__/____	__/__/____
						__/__/____	__/__/____
Concomitant products							
						__/__/____	__/__/____
						__/__/____	__/__/____
						__/__/____	__/__/____
						__/__/____	__/__/____

Action taken on the medication(s):
□ Drug (s) stopped □ Dose reduced □ Dose increased □ Dose not changed □ Monitoring increased □ Unknown □ Not applicable
Outcome of the suspected reaction after the action taken on the medication, including if the drug was later reintroduced:

C. Information about the ocular adverse event and any other adverse event

C. 1. Ocular adverse event:

I. Reaction Onset (DD/MM/YYYY):

II Describe reaction (please include any relevant tests/lab data):

	Left eye	Right eye		Left eye	Right eye
Pain	☐	☐	Low vision	☐	☐
Eye Discharge	☐	☐	Loss/Dimness of eyesight	☐	☐
Redness	☐	☐	Eye irritation and/or watering	☐	☐
Intolerance to light (photophobia)	☐	☐	Whitening of black part of the eye/ Cloudy appearance	☐	☐
Visual acuity test:	_____	_____			

III Any other ocular reaction?

(Please specify)

IV Were there any eye symptoms with previous treatment with miltefosine or another antileishmanial drugs?

If yes – please specify:

C. 2. Seriousness

I	Serious? ☐ Death ☐ Life-threatening ☐ Disability	☐ Hospitalization ☐ Congenital abnormality ☐ Other important medical event (please specify):

C. 3. Causality assessment as per the WHO-UMC system for standardised case causality assessment[2]

I	☐ Certain ☐ Probable/Likely ☐ Possible ☐ Unlikely ☐ Conditional/Unclassified ☐ Unassessable / Unclassifiable	Please provide rational for the assessment:

C. 4. Treatment of the ocular adverse event (if any)

I	**Treatment of ocular event**	Yes – No
	If yes, please specify:	**Professional consulted:** ☐ Ophthalmologist consulted. Date: ☐ Any other Healthcare professional (please specify):

II.	**Details on medicinal treatment:**

Product Name and Drug form (tablet etc.)	Dose/Unit	Route of admin.	Indication	Treatment started	Treatment stopped
				__/__/____	__/__/____
				__/__/____	__/__/____
				__/__/____	__/__/____
				__/__/____	__/__/____
				__/__/____	__/__/____

III.	**Other treatments, including surgical treatment:**

[2] https://who-umc.org/media/164200/who-umc-causality-assessment_new-logo.pdf

C. 5. Any other adverse event:

I. Reaction Onset (DD/MM/YYYY): II Describe suspected adverse drug reaction(s) in chronological order (e.g. symptoms, aggravation, laboratory reports, etc.):

D. Outcome of the event

I	Outcome of the treatment: ☐ Recovering ☐ Recovered ☐ Recovered with sequelae	 ☐ Not Recovered ☐ Unknown ☐ Died. Date of death (DD/MM/YYYY):

E. Medical History and any other relevant information

HIV (please specify)	Date of diagnosis: Antiretrovirals (dose and date): Viral load: CD4 count: Concomitant opportunistic infections such as CMV. Herpes virus, Toxoplasmosis etc.:
Tuberculosis (please specify)	
Diabetes (please specify)	
Hypertension (please specify)	
Trachoma (please specify)	
Any other condition/ relevant information:	

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F: Pre-prescription Eye Examination details, if available

F. 1. Before the treatment was started:

Was there any current diagnosed/undiagnosed eye problem?	Yes / No

If yes, what kind of eye problem?

	Left eye	Right eye		Left eye	Right eye
Pain	☐	☐	Low vision	☐	☐
Eye Discharge	☐	☐	Loss/Dimness of eyesight	☐	☐
Redness	☐	☐	Eye irritation and/or watering	☐	☐
Intolerance to light (photophobia)	☐	☐	Whitening of black part of the eye/ Cloudy appearance	☐	☐
Visual acuity test	_____	_____			

Please provide any other relevant information regarding pre-prescription ophthalmic examination:

G: Risk minimisation measures

I.	Was there a regular follow up of the patient? Yes / No If yes, how frequent? Was an eye examination performed at 4 weeks? Yes / No When was the last follow up? Date :
II	Was the patient and/or family members informed about the risks of ocular adverse event with miltefosine before starting the treatment? Yes / No Was the patient and/or family members advised to immediately stop the treatment by miltefosine and report to the nearest health centre or health worker if any ocular symptoms is noticed? Yes / No Were the patient and/or family members provided with a patient information brochure? Yes / No

III	Was the patient referred to an eye care facilities or ophthalmology services? Yes / No Date:
IV	Please provide any other relevant information regarding risk minimisation measures:

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Miltefosine and ocular events

Multidisciplinary technical group

Members of the MTG

Name	Expertise	Affiliation
Abraham Assefa	Tropical Diseases	Unit Head, Special Programme for Research & Training in Tropical Diseases (TDR), World Health Organization, Switzerland
Asim Sil	Ophtalmology	Medical Director, Netra Niramay Niketan, Vivekananda Mission Ashram, PO Chaitanyapur, Dist. Purba Medinipur, West Bengal, India
Bibhuti P. Sinha	Ophtalmology	Professor & Head Regional Institute of Ophthalmology, IGIMS-Patna, Bihar,India
Dinesh Mondal	Clinical specialist of Visceral Leishmaniasis, internal medicine, epidemiology	International Centre for Diarrheal Diseases, Bangladesh (Member of Leishmaniasis Expert Panel, WHO HQ)
Eduard E. Zijlstra	Post Kala-azar Dermal Leishmaniasis, Infectious Diseases and Tropical Medicine	Rotterdam Center for Tropical Medicine, Rotterdam, The Netherlands
Gerald Dal Pan	Pharmacology and Pharmacovigilance	Director, Office of Surveillance & Epidemiology, FDA's Center for Drug Evaluation and Research, US FDA, ACSoMP
Indranath Banerjee	Visceral Leishmaniasis and Field Epidemiology	Technical Specialist, CARE India, Patna, Bihar

Jochen Norwig	Pharmaceutical Quality, Pharmacopoeia and Pharmacogenomics	Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM)
Krishna Pandey	Visceral Leishmaniasis, internal medicines, Epidemiology	Director. Rajendra Memorial Research Institute of Medical Sciences (Indian Council of Medical Research) Department of Health Research, Patna, Bihar
Mira Desai	Pharmacology and Pharmacovigilance	Professor & Head, Pharmacology, NMC, Visnagar, Gujarat. Former Professor & Head, Pharmacology, BJ Medical College, Ahmedabad
Mitali Chatterjee	Pharmacology and Post Kala-azar Dermal Leishmaniasis	Professor, Institute of Postgraduate Medical Education & Research, Kolkata, India
Mourad Mokni	Leishmaniasis and Dermatology	Professor of dermatology, Faculty of Medicine University, University Tunis Al Manar 2, Tunisia
Mulugeta Russom	Pharmacist, pharmacoepidemiologist, and pharmacovigilance	Head, Eritrean Pharmacovigilance Centre, National Medicines and Food Administration, Medicines and Food Administration (NMFA), Eritrea
Nilima Kshirsagar (Chair)	Pharmacology and Pharmacovigilance	Emeritus Scientist, Former Chair Pharmacovigilance programme of India, ICMR, National Chair Clinical Pharmacology. Chairperson SAG BMS, Member SAB, ICMR, Govt of India.
Piero Olliaro	Visceral Leishmaniasis and Epidemiology	Professor of infectious diseases of poverty, Pandemic Sciences Institute, Nuffield Department of Medicine, University of Oxford, UK
Rogelio López-Vélez	Visceral Leishmaniasis	WHO CC (Member of Leishmaniasis Expert Panel, HQ) Unidad de Medicina Tropical, Servicio de enfermedades infecciosas, Hospital Universitario Ramón y Cajal, Madrid, Spain

Shyam Sundar	Internal medicines, Visceral Leishmaniasis and epidemiologist	Independent; Professor Emeritus, Banaras Hindu University (MF/PKDL trialist) (Member of Leish Expert Panel, HQ), Professor Emeritus, Internal Medicine, Banaras Hindu University, Varanasi, India
Simon Croft	Leishmaniasis	Professor of Parasitology in the Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine. London, WC1E 7HT, United Kingdom
Thomas Dorlo (Vice Chair)	Leishmaniasis, Pharmacometrician and clinical pharmacology	Senior Scientist, Antoni van Leeuwenhoek Hospital / Netherlands Cancer Institute, Drugs for Neglected Diseases initiative (DNDi)

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Miltefosine and ocular events

Multidisciplinary technical group

Executive summary

Executive Summary

Background

Miltefosine is an oral anti-infective and one of the medicines with established efficacy in the treatment of some clinical forms of leishmaniasis, a parasitic infection spread by sandflies. Following reports of serious ocular events in patients treated by miltefosine for post-kala-azar dermal leishmaniasis (PKDL), the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) and the SEARO[3] Regional Technical Advisory Group on Visceral Leishmaniasis expressed concerns and requested the WHO to establish a multidisciplinary technical group of experts.

The WHO established an international multidisciplinary technical group (MTG)[4] to review, evaluate and interpret all available safety data related to ocular adverse event associated with the use of miltefosine in leishmaniasis and provide WHO with:

1. a scientific advice on the possible causal relationship between miltefosine and associated ocular adverse events,
2. recommendations on the need to update risk minimization measures and, if needed, details on such recommended measures including how their effectiveness will be measured,
3. recommendations on risk communication to patients and healthcare professionals,
4. recommendations on the need for further studies to address remaining uncertainties, and if so, advice on their design to address these uncertainties

The MTG met on 10 October, 2 November and 30 November 2022, and adopted its final recommendations in December 2022, which were presented to ACSoMP on 14 December 2022.

[3] WHO Regional Office for South-East Asia.

[4] Please refer to the MTG terms of reference and the list of members.

Method

To facilitate the work from the MTG, the WHO was supported by the German National Regulatory Authority (BfArM) and the Uppsala Monitoring Centre (UMC) which collected and compiled all available evidence and information on the causal relationship between reports of serious ocular events and exposure to miltefosine and assisted in incorporating the comments from the MTG. Especially, a literature review was conducted, and information were requested and obtained from Disease programmes, Pharmacovigilance programmes, National Regulatory Authorities, the Marketing Authorisation Holders (MAH) of the originator medicinal product, and researchers with known ongoing/unpublished clinical studies using miltefosine, and all information available in the WHO global pharmacovigilance database VigiBase were analysed. The quality of the originator and one generic product used in India were analysed by the BfArM and the Indian Pharmacopoeia Commission. The MTG was also appraised of the experience gained from India's disease programme, and especially three field visits focusing on patients who experienced ocular adverse events following treatment with miltefosine. The MTG was also provided with an opportunity to audition the MAHs and discuss their conclusions.

Results

Ocular involvement of the different clinical forms of leishmaniasis have been described in humans (such as conjunctivitis, eyelid involvement, retinal disorders, and rarely keratitis), and in different animal species (dogs, cats, mice, hamster and guinea pigs).

Analytical results of miltefosine-containing products conducted by the BfArM and the Indian Pharmacopoeia Commission did not provide any indication that the tested products were of a considerably reduced pharmaceutical quality or unsafe for human use.

In non-clinical studies, ocular adverse reactions following administration of miltefosine were reported in rats, especially retinal atrophy. A non-clinical ophthalmological study also reported dose- and time-dependent changes partially reversible in high-dose. No ocular changes were observed in dogs.

In humans, 114 case reports were identified from VigiBase, three field studies conducted in India, and the literature. In a majority of the cases[5], a causal relationship between the observed ocular event and the intake of miltefosine was considered to be possible. These cases included two with a positive re-challenge, one of which with a twice positive re-challenge, and two cases of negative rechallenge. One case of keratitis after 27-day miltefosine therapy was also identified despite a negative skin biopsy for Leishman-Donavan bodies, which may point to a direct effect of miltefosine without underlying PKDL.

[5] Causality could be assessed for 83 cases.

Despite a much larger exposure to miltefosine[6], only a small number of reactions (n=5) were reported among all available cases for patients with visceral leishmaniasis (VL) and suggested a milder reaction.

Ocular symptoms, including keratitis, keratopathy and acute scleritis, uveitis, ocular hyperaemia (increased ocular vascularity) and visual impairment up to blindness, developed between a few days and several weeks following the initiation of treatment, in both men and women, including in children under 18-year-old (the youngest patient being 8-year-old). The vast majority of the cases related to treatment for PKDL in South Asia[7], which may suggest that PKDL is a predisposition factor for the observed adverse ocular effects with miltefosine. The majority (68%) of the ocular adverse events that have been assessed at least possibly related to miltefosine in relation to the administration of Miltefosine occurred beyond the 28 days of treatment[8] recommended in the product information. When the information was available, most of the cases resolved (sometime partly resolved) after miltefosine was withdrawn, sometimes after treatment with steroids (mostly eye drops, sometimes oral) and topical antibiotics and/or further medication was started. However, in some cases including loss of vision, the adverse ocular event persisted after miltefosine was withdrawn. No further risk factor could be identified.

The frequency of adverse ocular event during treatment with miltefosine could not be estimated (due to limitations such as the size of the available studies, uncertainty about underreporting, and the absence of a comparator group), and the mechanism that may cause keratitis and other ocular adverse reactions in the context of miltefosine antileishmanial therapy remains unclear.

Regarding other drugs used in the treatment of leishmaniasis, 168 reports were found in VigiBase[9] with PKDL as indication of suspect/interacting drug. Only 3 reports had no relation to miltefosine (liposomal amphotericin B used instead), including one report with ocular events. Overall, the ocular lesions observed with miltefosine have been rarely described with any other anti-leishmanial drug.

Conclusions and Recommendations

Based on the available data, a causal relationship between ocular adverse events and the exposure to miltefosine is at least a reasonable possibility. The risk of ocular adverse events has been observed mostly during the treatment of patients with PKDL in South Asia in both men and women, including in children under 18-year-old, and mostly beyond 28 days of treatment. No further risk factor could be identified. When the information was available, most of the cases resolved after miltefosine was

[6] Between 2004 and the end of 2013 (i.e. before the new treatments emerged) about 300,000 patients with VL have been treated with miltefosine in India (28 days treatment then recommended). Between 2014 and 30/09/2022, 8,633 patients with PKDL were treated with miltefosine in India (12 weeks treatment recommended).
[7] The evidence was not sufficient to confirm or rule out whether a similar risk may be expected in African PKDL, considering important differences in clinical characteristics, personal risk factors, healthcare systems, and treatment guidelines.
[8] Clinical guidelines generally recommend 12 weeks of treatment for PKDL in South Asia.
[9] Data lock point: 9 October 2022.

withdrawn, sometimes after a treatment was started. However, in some cases, the adverse ocular event led to permanent loss of sight. The frequency of adverse ocular event during treatment with miltefosine could not be estimated, and the mechanism of action remains unclear. As a precautionary measure, and although the risk appears to be mostly reported in patients with PKDL in South Asia, the below recommendations should also be considered in other patients exposed to miltefosine.

In order to minimise the risks of ocular adverse events in patients exposed to miltefosine, the MTG recommended to include a warning and to list the ocular adverse events in the SmPC and the patient information leaflet. In addition, the MTG provided guiding principles for the prevention, early detection and management of eye complications in patients treated with miltefosine. The MTG also recommended that a patient information brochure based on MTG recommendations is developed by WHO to facilitate risk communication. The MTG further requested that the WHO publishes a communication on its website, encourages the communication of these conclusions through disease programmes, and inform investigators of identified ongoing clinical trials. In countries where it is feasible, a Direct Healthcare Professional Communication may also be considered by the National Regulatory Authority. The MTG finally recommended the use of active surveillance, supported by a follow-up questionnaire, to further characterise the risk and its frequency, and to assess the effectiveness of the risk minimisation measures. The MTG also considered that a study analysing miltefosine pharmacokinetics, the presence of parasites, and immune reaction in patients with PKDL could be helpful to assess the specificity and causality of this adverse event in those patients.

Acknowledgment

This work was made possible thanks to the active support and collaboration from the National Centre for Vector Borne Disease Control and the Pharmacovigilance Programme of India, the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM), the Uppsala Monitoring Center, as well as Disease and Pharmacovigilance programmes and National Regulatory Authorities in several WHO regions, and WHO country offices, regional offices, and headquarters.

World Health Organization

Miltefosine and ocular events

Multidisciplinary technical group

Conclusions and Recommendations

MTG Conclusions

Leishmaniasis and ocular events

Ocular involvement of leishmaniasis have been described in humans with visceral leishmaniasis (VL: retinal findings, conjunctivitis[10]), cutaneous leishmaniasis (CL: adnexa, conjunctivitis and episcleritis, keratitis[11]), mucocutaneous leishmaniasis (MCL: adnexa and anterior segments of the eye[12]), and Post-Kala-Azar Dermal Leishmaniasis (PKDL: conjunctivitis, blepharitis and uveitis[13]). Furthermore, ocular symptoms of leishmaniasis (incl. keratitis) were also seen in different animal species (dogs, cats, mice, hamster and guinea pigs).

Scorza et al. 2017 postulates that various *Leishmania* species cause activation of human skin keratinocytes. Specifically, *L. donovani*, which causes PKDL, induced a significantly greater transcript of proinflammatory IL-6 genes than controls in an in-vitro assay. If corneal keratocytes would be equally affected this might explain corneal ocular adverse reaction seen with miltefosine in patients with PKDL.

Quality of the products

The originator miltefosine product Impavido and the generic product Vartefos have been assessed with regard to their pharmaceutical quality by the BfArM laboratory and the Indian Pharmacopoeia Commission. No significant deviation was observed in both samples from the specifications described in the licensing dossier as well as the International Pharmacopoeia's draft monograph on miltefosine capsules. Additional investigation conducted by the BfArM to search for the presence of unknown spectroscopic features did not find any abnormality. Analytical results of miltefosine-containing

[10] Maude et al 2014, ModarresZadeh et al. 2006
[11] ModarresZadeh et al. 2006; Satici et al 2004, Cairns 1968
[12] Wunderle 2002
[13] El Hassan et al 1998

products did not provide any indication that the tested products were of a considerably reduced pharmaceutical quality or unsafe for human use.

Non-clinical

In an 8-weeks non-clinical study in rats adverse reactions such as red incrustations around the nostrils and eyes as well as retinal atrophy (degeneration and necrosis of the outer granular layer) have been seen. In a 52-week non-clinical study ophthalmology changes with enlarged choriocapillaris vessels, thinned retinal vessels, lens opacities and retinal degeneration etc. were observed under miltefosine. These changes occurred in a dose- and time-dependent manner and were partially reversible in high-dose recovery animals except the severe changes. No ocular changes were observed in dogs.

Clinical safety

Case reports associated with miltefosine

114 case reports were identified, including 75 reports from VigiBase[14], further 25 reports from the field studies in India, 3 cases from EudraVigilance, as well as 11 literature reports (after excluding duplicates). In a majority of the cases[15], a causal relationship between the observed ocular event and the intake of miltefosine was considered to be possible as per the WHO-UMC system for standardised case causality assessment. These cases included two with positive re-challenge (Khatri et al. 2020, Saurabh and Mahabir 2019), one of which with a twice positive re-challenge. In addition, two cases of negative rechallenge were reported. In one of the negative rechallenge cases, medication was discontinued for 113 days before reintroduction and no reoccurrence was reported 23 days after restarting the treatment with miltefosine. In the other negative rechallenge case, the time between the initial withdrawal and restarting of miltefosine was unclear, as well as how long was the follow up period of the patient at the time of reporting. One case of keratitis after 27-day miltefosine therapy was also identified despite a negative skin biopsy for Leishman-Donavan bodies, which may point to a direct effect of miltefosine without underlying PKDL.

Ocular symptoms, including keratitis, keratopathy and acute scleritis, uveitis, ocular hyperaemia (increased ocular vascularity) and visual impairment up to blindness, developed between a few days to several weeks following the initiation of treatment, in both men and women, including in children under 18-year-old (the youngest patient being 8-year-old). The vast majority of the cases related to treatment for PKDL in South Asia[16], which may suggest that PKDL is a predisposition factor for the observed

[14] including 3 reports with uncoded reactions. Data lock point: 9 October 2022.
[15] Causality could be assessed for 83 cases.
[16] The evidence was not sufficient to confirm or rule out whether a similar risk may be expected in African PKDL, considering important differences in clinical characteristics, personal risk factors, healthcare systems, and treatment guidelines.

adverse ocular effects with miltefosine. Despite a much larger exposure to miltefosine[17], only a small number of reactions (n=5) were reported among all available cases for patients with VL and suggested a milder reaction and included ocular hyperaemia (n=3), eye pain (n=1), and mydriasis (n=1).

From the cases which have been assessed at least possibly related to miltefosine by BfArM and/or the UMC, the ocular adverse events occurred after a treatment of 0 to 28 days in 13 cases (11 from VigiBase and 2 additional from the literature), whereas 32 cases (9 from literature and further 23 from VigiBase) had a time-to-onset (TTO) of over 28 days. In two further cases assessed at least possibly related to miltefosine no TTO could be estimated. The reported range of TTO was compatible with the development of the adverse effects observed. Generally, in cases with shorter TTO or treatment duration (28 days or less) the ocular reaction appeared to be less serious (e.g., ocular hyperaemia, eye irritation, eye swelling) than in cases with a longer TTO/treatment duration. Most of the cases resolved (sometime partly resolved) after miltefosine was withdrawn, sometimes after a treatment with steroids (mostly eye drops, sometimes oral) and topical antibiotics and/or further medication was started. However, in some cases, the adverse ocular event led to permanent loss of sight. Furthermore, effects of miltefosine on the retinal pigment epithelium were reported in humans treated with miltefosine 150 mg/day for advanced metastatic colorectal or lung cancer [Theischen et al., 1993]. No further risk factor could be identified.

Frequency

The frequency of adverse ocular event during treatment with miltefosine could not be estimated due to the limitations of the available evidence, including the size of the studies, uncertainty about the scale of underreporting, and the absence of a comparator group of South Asian patients with PKDL treated without miltefosine.

Mechanism of action

Various potential mechanisms for the observed ocular adverse effects may be theoretically assumed: i) accumulation in the corneal stroma due to protonation of the drug's phosphocholine head group in lysosomes after entry into cells and a direct toxic effect or ii) an immune response triggered by miltefosine induced parasite killing and subsequent release of parasite antigen as well as iii) ocular reactions due to a local Leishmania infection. The finding that lesions often resolved with topical corticosteroids may point to an immune system-mediated mechanism or at least an involvement of the immune system. However, these assumptions remain theoretical and the mechanism that may cause keratitis and other ocular adverse reactions in the context of miltefosine antileishmanial therapy remains unclear.

[17] Between 2004 and the end of 2013 (i.e. before the new treatments emerged) about 300,000 patients with VL have been treated with miltefosine in India (28 days treatment then recommended). Between 2014 and 30/09/2022, 8,633 patients with PKDL were treated with miltefosine in India (12 weeks treatment recommended).

Other antileishmanial drugs

Regarding other drugs in the treatment of leishmaniasis, 168 reports were found in VigiBase[18] with PKDL as indication of suspect/interacting drug. In 163 reports, miltefosine was reported as suspect/interacting drug, in 1 report as concomitant drug, in 1 report with uncoded suspect/interacting drug but reported as "miltefosina". Only 3 reports had no relation to miltefosine (liposomal amphotericin B used instead), including one report with ocular events: ulcerative keratitis, corneal infiltrates, corneal neovascularization, and blindness[19].

In general, the ocular lesions observed with miltefosine have been rarely described with any other anti-leishmanial drug.

MTG Recommendations

Based on the available data, a causal relationship between ocular adverse events and the exposure to miltefosine is at least a reasonable possibility. The risk of ocular adverse events has been observed mostly during the treatment of patients with PKDL in South Asia in both men and women, including in children under 18-year-old, and mostly beyond 28 days of treatment. Most of the cases resolved (sometime partly resolved) after miltefosine was withdrawn, sometimes after a treatment with steroids (mostly eye drops, sometimes oral) and topical antibiotics and/or further medication was started. However, in some cases, including loss of vision, the adverse ocular event persisted after miltefosine was withdrawn. No further risk factor could be identified. The frequency of adverse ocular event during treatment with miltefosine could not be estimated, and the mechanism that may cause keratitis and other ocular adverse reactions in the context of miltefosine antileishmanial therapy remains unclear.

As a precautionary measure, and although the risk appears to be mostly reported in patients with PKDL in South Asia, the below recommendations should also be considered in other patients exposed to miltefosine.

Risk minimisation measures

In order to minimise the risks of ocular adverse events in patients exposed to miltefosine, the MTG recommended to include a warning and to list the ocular adverse events in the SmPC and the patient information leaflet (please refer to Annex 1).

In addition, the MTG provided the below guiding principles for the prevention, early detection and management of eye complications in patients treated with miltefosine (please refer to Annex 2).

Risk communication

[18] Data lock point: 9 October 2022.

[19] No ocular event was reported in the two other cases.

The MTG recommended that a patient information brochure based on MTG recommendations is developed by WHO to facilitate risk communication. The MTG further requested that the WHO publishes a communication on its website, encourages the communication of these conclusions through disease programmes, and inform investigators of identified ongoing clinical trials. In countries where it is feasible, a Direct Healthcare Professional Communication may also be considered by the National Regulatory Authority.

Remaining uncertainties and need for further studies

The MTG finally recommended the use of active surveillance, supported by a follow-up questionnaire (please refer to annex 3), to further characterise the risk and its frequency, and to assess the effectiveness of the risk minimisation measures.

The MTG also considered that a study analysing miltefosine pharmacokinetics, the presence of parasites, and immune reaction in patients with PKDL could be helpful to assess the specificity and causality of this adverse event in those patients.