SAFETY ALERT

DRAP SAFTEY ALERT NO. 46

Safety Alert of Risk of Ocular Adverse Events with Miltefosine.

Date: 24th of April, 2024.

Target Audience:

- Manufacturers and importers of Miltefosine;
- Healthcare Professionals; and
- Patients, Consumers or Caregivers.

Background.

The World Health Organization (WHO) through its medical product alert dated 12th April 2023 informed healthcare professionals and regulatory authorities about the risk of ocular adverse events in people who have taken miltefosine and provided advice on measures to minimize this risk in patients exposed to miltefosine. Following reports of ocular disorders following miltefosine use originating mostly from South Asia, the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) recommended the WHO to investigate this issue further. The proposed method was discussed in June 2022 and WHO established an ad-hoc Multidisciplinary Technical Group (MTG) to advise on the causality, the risk characteristics and frequency, risk minimisation measures, risk communication, remaining uncertainties and the need for further studies. The MTG was also supported by the WHO, the German National Regulatory Authority (BfArM) and the Uppsala Monitoring Centre (UMC).

Based on the available data, the MTG considered that a causal relationship between ocular adverse events and 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 Post-Kala-Azar Dermal Leishmaniasis (PKDL) in South Asia in both men and women, including in children under 18 years old, and mostly beyond 28 days of treatment. No further risk factors could be identified. When the information was available, most of the cases were resolved after miltefosine was withdrawn, sometimes after a symptomatic treatment was started.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.

Previously, the ACSoMP discussed during its meeting on 14th of December 2022 the issue of ocular adverse events with miltefosine and *inter-alia* advised 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 along with the issuance of Direct Healthcare Professional Communication by National regulatory authorities.

Post-Kala-Azar Dermal Leishmaniasis (PKDL) is a sequela which can generally occur 6 months to several years after the 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 Southeast Asia.

Action in Pakistan.

The case was discussed in the 4th meeting of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) of the DRAP held on 26th of February, 2024 which decided the case as per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022, that registration holders should update the prescribing information/ label of Miltefosine-containing medicines by including information in the warning and precaution section about the risk of ocular adverse events and also list these in adverse drug reaction section. As per Rule 10 (1) (b) of Pharmacovigilance Rules, 2022 recommended the National Pharmacovigilance Centre to issue a safety alert/advisory related to the risk of ocular adverse events with Miltefosine-containing medicines.

Therapeutic Good.

Name: **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).

Advice for Healthcare Professionals.

The following is advised to 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.

Advice for Patients.

Patients are advised to consult their doctors if they experience any sort of reaction/problem in their eyes after the start of the miltefosine treatment and also inform healthcare professionals about any pre-existing eye diseases.

Guidelines for reporting Adverse Drug Reactions (ADRs).

Both healthcare professionals and patients are requested to report any suspected adverse drug reaction (ADRs) with miltefosine to the National Pharmacovigilance Centre (NPC), Drug Regulatory Authority of Pakistan (DRAP) through the Med Vigilance E-Reporting System available on the DRAP website. Similarly, ADRs can also be reported through Med Safety App which is available for download from the App Store (for iOS devices) and Google Play (for Android devices).

References.

- Minutes of 4th meeting of Pharmacovigilance Risk Assessment Expert Committee, DRAP.
- WHO Advisory Committee on Safety of Medicinal Products (ACSoMP): Measures to minimize the risk of ocular adverse events with miltefosine.