# Miltefosine

Section: 6. Anti-infective medicines > 6.5. Antiprotozoal medicines > 6.5.2. Antileishmaniasis medicines

EMLc | ATC codes: P01CX04

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| **Indication** | Visceral leishmaniasis ICD11 code: 1F54.0 |
| **INN** | Miltefosine |
| **Medicine type** | Chemical agent |
| **List type** | Core |
| **Formulations** | **Oral > Solid:** 10 mg ; 50 mg |
| **EML status history** | First added in 2011 (TRS 965) |
| **Sex** | All |
| **Age** | Also recommended for children |
| **Therapeutic alternatives** | The recommendation is for this specific medicine |
| **Patent information** | Patents have expired in most jurisdictions<br>Read more about patents. |
| **Wikipedia** | Miltefosine |
| **DrugBank** | Miltefosine |

## Summary of evidence and Expert Committee recommendations

An application was submitted by Paladin Labs Barbados, the manufacturer of miltefosine, for its inclusion on the WHO Model List of Essential Medicines for the treatment of cutaneous and visceral leishmaniasis in adults and children. A previous application was considered in 2005 but at that time, the Committee did not recommend its inclusion due to lack of information about the pharmacokinetic profile in humans; a lack of efficacy and safety data for the treatment of cutaneous leishmaniasis; a lack of dosing information and safety data for its use in visceral leishmaniasis; and the need for comparative cost– effectiveness data, including a comparison with liposomal amphotericin B. The application did not provide a search strategy or reference existing systematic reviews. Data were presented in relation to visceral leishmaniasis (6 studies, 2 of which were RCTs), cutaneous leishmaniasis (4 studies, including 3 RCTs) and mucosal leishmaniasis (1 observational study). In visceral leishmaniasis, miltefosine was superior to amphotericin B, and similar to antimony but less toxic; in the studies in cutaneous leishmaniasis, miltefosine was superior to placebo and similar or superior to antimonials, again with less toxicity. The Committee noted that there were no comparative trials of miltefosine with either liposomal amphotericin B or paromomycin. For combination treatment, the evidence was based on one trial published in the Lancet (1). This was a randomized four-arm comparison of amphotericin B (n=157), miltefosine + liposomal amphotericin B (n=160), paromomycin + liposomal amphotericin B (n=155), or miltefosine + paromomycin (n=158). The trial was designed as a non-inferiority comparison and on the basis of the per-protocol analysis there was no difference between the treatment options. On the basis of the intention to treat population, all combinations are probably superior to conventional amphotericin alone. The Committee noted that studies in animals have shown reproductive toxicity so that miltefosine is currently contraindicated for use in pregnant women. The European Medicines Agency (EMA) has assessed the risk of teratogenic effects as requiring women of childbearing potential to use effective contraception during and up to three months after treatment. Paladin’s pharmacovigilance group

has received no reports of any birth defects since the first regulatory approval of miltefosine. From November 2004 until March 2009, 62 659 treatment courses have been supplied either for clinical trials, government treatment programmes, or individual use. Evidence showing the comparative cost–effectiveness of current leishmaniasis treatment strategies was comprehensively summarized in the application. The data presented suggest that treatment with miltefosine is the least expensive, with the exception of paromomycin. The Committee was informed that the Department of Control of Neglected Tropical Diseases held a WHO Expert Committee Meeting on Leishmaniasis in 2010 (published as WHO Technical Report Series, No. 949). The report of the meeting includes many recommendations on treatment, including recommendations on the use of miltefosine. It also recommends the use of combination treatment for visceral leishmaniasis. This report is the basis of the recommendation from the Department for inclusion of miltefosine in the WHO Model List. The Department has also recommended that a note be included in the List that for visceral leishmaniasis caused by L. donovani, miltefosine, paromomycin, and antimonials should only be used in combination therapy. The report of the Expert Committee does not provide full details of the basis for the recommendation as it does not contain references. Based on evidence of efficacy and safety in the treatment of visceral leishmaniasis in both adults and children, and evidence of efficacy and safety in the treatment of adults in cutaneous and mucosal leishmaniasis, the Committee decided to add miltefosine to the WHO Model List for both adults and children. Due to the teratogenic risks of miltefosine treatment a note should be added to the listing indicating that it should not be used in women of childbearing age unless contraception can be guaranteed for the duration of treatment and three months afterwards. The Committee did not recommend a note concerning combination treatment until there is more evidence of the potential advantages over single component treatment. The Committee was informed about agreements on a pricing structure and preferential pricing for developing countries. Compliance with this agreement needs to be monitored. (1) Sundar S et al. Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomised controlled trial. The Lancet, 2011, 377(9764):477–486.

