

DATA SHEET

LAMPRENE[®] Clofazimine 50 or 100 mg Capsules, Soft

Description and composition

Pharmaceutical form

Capsules, soft.

Active substance

Each capsule contains 50 or 100 mg of micronized clofazimine suspended in an oil-wax base.

Excipients

Butylated hydroxytoluene (E 321), Citric acid anhydrous (E330), Propylene glycol, Rapeseed oil, refined, Soybean lecithin, Beeswax, yellow, Soybean oil, hydrogenated, Partially hydrogenated vegetable oils

Capsule shells

Ethyl hydroxybenzoate sodium (E215), Propyl parahydroxybenzoate sodium, Ethylvanillin, Gelatin, Glycerol 85% (E422), Black iron oxide (E172), Red iron oxide (E172), p-Methoxy acetophenone

Indications

Lamprene[®], employed in combination with rifampicin and dapsons, is indicated as treatment for multibacillary (MB) forms of leprosy:

- for all types of leprosy with positive skin smear,
- for all cases clinically diagnosed as multibacillary with more than 5 skin lesions,
- for all cases of relapse of previously treated multibacillary leprosy;
- as well as for erythema nodosum leprosum (ENL). Multidrug therapy (MDT) is necessary in order to prevent the emergence of resistant strains of *Mycobacterium leprae*.

Note that MDT calendar blister packs and bulk Lamprene capsules for management of ENL reactions can be obtained free of charge from the WHO.

Dosage and administration

For the treatment of leprosy the WHO recommends the following regimens:

Multibacillary leprosy

Table 1

	Dapsone	Rifampicin	Clofazimine (Lamprene)
Adults and adolescents (50 to 70 kg)	100 mg once daily as self medication	600 mg once a month under supervision	50 mg once daily as self medication AND 300 mg once a month under supervision
Children (10 to 14 years)	50 mg once daily as self medication	450 mg once a month under supervision	50 mg on alternate days as self medication AND 150 mg once a month under supervision

This triple combination should be given for 12 months (i.e. 12 cycles of therapy). An additional 12 months of this triple combination may be necessary for MB patients showing evidence of relapse.

Paediatric population (Children below 10 years): The dose should be adjusted according to body weight: 1 to 2 mg/kg clofazimine + 10 to 20 mg/kg rifampicin + 1 to 2 mg/kg dapsone. As an example, Lamprene (clofazimine) 100 mg once a month under supervision + 50 mg twice a week as self-medication + rifampicin 300 mg once a month under supervision + dapsone 25 mg once a day as self-medication.

Patients with Erythema nodosum leprosum (ENL)

Adults and children: If the patient develops ENL, the treatment with rifampicin and dapsone should be continued as before, and the dosage of Lamprene raised to 200 to 300 mg daily, given under medical supervision. These high daily doses should not be given for longer than 3 months (see section 6 Warnings and precautions). The dose of clofazimine should be gradually reduced to 100 mg twice a day for 12 weeks and then 100 mg once a day for 12 to 24 weeks.

Method of administration

To ensure maximum absorption Lamprene should be taken with meals or with milk.

Dosing in special populations

Patients with concomitant HIV infection: Information available from HIV-positive and immunocompromised leprosy patients indicates that the response to MDT, including treatment of reactions, is not altered and that no dose adjustments are required in these patients.

Contraindications

Known hypersensitivity to clofazimine or to any of the excipients of Lamprene.

Warnings and precautions

Lamprene should never be used alone for the treatment of leprosy. Clofazimine must be used in combination with rifampicin and dapsone according to the dosing regimens described in "Dosage and administration". Multidrug therapy is necessary to prevent the emergence of drug resistance. Patients should be informed of the importance of compliance with the prescribed drug regimen in the prevention of the occurrence of drug resistance. Irregularity in administration of medication and poor compliance can lead to delayed and incomplete cure, rendering the patient a source of contamination. Poor compliance can ultimately result in the development of disabilities and deformities. Whenever possible, efforts should be made, to ensure that non-compliant patients receive adequate assessment, health education and supervised treatment.

Patients should be trained in recognizing the signs and symptoms of reactions and relapses following completion of treatment, and should be made aware of the importance of immediately reporting earliest manifestations of these signs to the relevant health centres.

Some data indicate a trend towards reduction in the frequency and severity of ENL (Erythema Nodosum Leprosum) in MB leprosy patients treated with MDT. This trend may be attributed to the anti-inflammatory properties of clofazimine. Nevertheless, temporary, unexplained increases in the reporting of reversal reactions have also been observed in MB leprosy patients, usually during the first year of treatment with MDT. WHO generally recommends not to interrupt MDT during lepra reactions. Please refer Dosage and administration for Lamprene dosing in patients who develop ENL reactions. Lepra reactions usually respond satisfactorily to standard anti-inflammatory therapy (prednisolone).

Warnings

Clofazimine has an heterogeneous distribution throughout the body and a slow elimination rate, accumulating mainly in fatty tissue, reticuloendothelial system (macrophages, histiocytes and spleen) and skin. Adverse reactions to clofazimine are mainly linked to its uptake by tissue and organs. Because of this, the use of high doses for long periods should be avoided. Daily doses of greater than 100 mg Lamprene should be given for as short a time as possible (<3 months) and only under close medical supervision. After prolonged administration in high doses, clofazimine may accumulate in various organs, body fluids and tissues. Among the viscera, the jejunum has the highest drug depositions, closely followed by the spleen. The deposition of large amounts of clofazimine in the intestinal mucosa cause irritation, leading to gastrointestinal disturbances (e.g. abdominal pain (sometimes intermittent), nausea, vomiting and diarrhoea), usually with mild forms, but sometimes with more severe clinical manifestations. If crystals are deposited in the mesenteric lymph nodes and/or histiocytes at the lamina propria of the jejunal mucosa, this might lead to intestinal obstruction. If gastrointestinal symptoms develop during treatment, the dosage should be reduced or the interval between doses prolonged. Symptoms may slowly regress on withdrawal of the drug.

In the event of persistent diarrhoea or vomiting, the patient should be hospitalised.

Precautions

If possible, leprosy patients suffering repeatedly from abdominal pains and diarrhoea, as well as those with liver or kidney damage, should not be treated with Lamprene. If treatment is necessary, these patients should be kept under medical supervision.

Physicians should be aware that skin discoloration due to clofazimine may result in depression (two cases of depression with suicide have been reported). Patients should be warned that Lamprene may cause discoloration of the conjunctiva, lacrimal fluid, sweat, sputum, urine, faeces, nasal secretions, semen, breast milk and reddish to brownish-black

discoloration of the skin. Patients should be told that discoloration of the skin, although reversible, may take several months or years to disappear after the end of therapy with Lamprene.

Driving and using machines

Dizziness, decreased visual acuity, fatigue and headache have been reported under Lamprene therapy. Patients experiencing such adverse reactions should not drive a vehicle or operate machines.

Adverse drug reactions

Adverse drug reactions (Table 2) are listed according to system organ classes in MedDRA. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse drug reaction: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$) very rare ($< 1/10,000$), including isolated reports.

Table 2

Blood and lymphatic system disorders	
Very rare:	Lymphadenopathy, splenic infarction, anaemia]
Psychiatric disorders	
Very rare:	Depression
Nervous system disorders	
Uncommon:	Headache
Very rare:	Dizziness
Eye disorders	
Very common:	Conjunctival discolouration, corneal pigmentation, tear discolouration
Common:	Visual acuity decreased, dry eyes, eye irritation
Uncommon:	Maculopathy, corneal deposits
Respiratory, thoracic and mediastinal disorders	
Very common:	Sputum discoloured
Gastrointestinal disorders	
Very common:	Nausea, vomiting, abdominal pain, diarrhoea, faeces discoloured
Uncommon:	Gastroenteritis eosinophilic, anorexia
Very rare:	Intestinal obstruction, gastrointestinal haemorrhage, abdominal discomfort, abdominal pain upper, constipation
Hepatobiliary disorders	
Very rare:	Hepatitis, blood bilirubin increased, jaundice, aspartate aminotransferase increased
Skin and subcutaneous tissue disorders	
Very common:	Sweat discolouration, skin discolouration, hair colour changes, ichthyosis, dry skin
Common:	Rash, pruritus
Uncommon:	Photosensitivity reaction, dermatitis acneiform

Very rare:	Dermatitis exfoliative
Renal and urinary disorders	
Very common:	Chromaturia
General disorders and administration site conditions	
Uncommon:	Fatigue
Very rare:	Pyrexia
Investigations	
Common:	Weight decreased
Uncommon:	Blood sugar increased

Note: Depression was reported to be due to skin discolouration and two suicides were reported. Reddish to brownish-black discoloration of the skin and leprosy lesions, particularly in fair-skinned patients at sites exposed to light, and discoloration of the hair are reversible, although in the case of the skin it may take several months to disappear after the end of treatment. The corneal pigmentation (subepithelial corneal brownish pigmented lines) is due to crystal deposits. It is reversible on discontinuation of Lamprone. Some of the adverse reactions to clofazimine are mainly linked to its uptake by tissue and organs (see Warnings and precautions).

Interactions

Dapsone

Lamprone seems to have no important effects on the pharmacokinetics of dapsone, although a transient increase in the urinary excretion of dapsone occurred in a few patients. Preliminary data suggesting that dapsone inhibits the anti-inflammatory activity of Lamprone have not been confirmed. If leprosy-associated inflammatory reactions develop in patients being treated with dapsone and Lamprone, it is still advisable to continue treatment with both drugs.

Rifampicin

Clofazimine reduces rifampicin absorption in leprosy patients, increasing the time it takes for peak serum concentration to be reached and prolonging the elimination half-life. Bioavailability was not affected, so this interaction is unlikely to be clinically significant.

Isoniazid

In patients receiving high doses of clofazimine (300 mg daily) and isoniazid (300 mg daily), elevated concentrations of clofazimine were detected in plasma and urine, although skin concentrations were found to be lower.

Pregnancy and breast-feeding

Pregnancy

It is generally considered that the benefits of MDT (including Lamprone) in the treatment of leprosy during pregnancy outweigh any potential risk and since leprosy is exacerbated during pregnancy, WHO recommends that treatment with MDT should be continued during pregnancy.

No mutagenic activity was detected in cytogenetic tests in patients treated with Lamprene. Experience with Lamprene in pregnancy is limited. Clofazimine crosses the placenta, and skin discoloration in neonates has been observed.

Breast-feeding

The benefits of MDT treatment in lactating mothers clearly outweigh the risks, therefore WHO recommend that treatment be continued during lactation.

Clofazimine passes into the breast milk, and skin discoloration may occur in the infant.

Overdosage

No specific data are available on the treatment of overdose with Lamprene. In cases of acute overdose the stomach may be emptied by inducing vomiting or performing gastric lavage, and symptomatic treatment may be given as required.

Clinical pharmacology

Pharmacotherapeutic group: Antileprosy drug, ATC code: J04BA01.

Pharmacodynamic properties (PD)

The major role of the dapsone-clofazimine component of the MDT regimen for MB leprosy is to ensure the elimination of the spontaneously occurring rifampicin-resistant mutants (estimated to be $\leq 10^4$ organisms in an untreated patient with lepromatous leprosy). Daily treatment with dapsone-clofazimine alone for 3 months killed >99.999% of viable *Mycobacterium leprae*, suggesting that all spontaneously occurring rifampicin-resistant mutants are likely to be eliminated by 3 to 6 months of treatment with the dapsone-clofazimine component of the MDT regimen.

Clofazimine exerts in man a bacteriostatic and weakly bactericidal effect on *Mycobacterium leprae* (*M. leprae*, Hansen's bacillus). Its precise mechanism of action against mycobacteria remains to be elucidated. Clofazimine appears to bind preferentially to mycobacterial DNA and inhibit mycobacterial replication and growth.

No cross-resistance occurs with dapsone and rifampicin, probably because clofazimine has a different mode of action. *M. leprae* resistant to clofazimine have been reported only in isolated cases.

The minimum inhibitory concentration of clofazimine for *M. leprae* in mouse tissue has been estimated at between 0.1 and 1 microgram per gram; uneven tissue distribution precludes a more accurate estimate. In patients with lepromatous leprosy, the overall antibacterial effect of Lamprene is comparable to that of dapsone. However, the onset of antimicrobial activity of Lamprene is slow and can only be demonstrated after about 50 days of therapy.

Clofazimine also displays an anti-inflammatory effect, which may contribute to the efficacy of Lamprene in controlling ENL reactions.

Pharmacokinetic properties (PK)

Absorption

Clofazimine is absorbed relatively slowly. Bioavailability of clofazimine from the micronised suspension in an oil-wax base (such as that of the Lamprene capsules) is up to 70% after a dose of 100 mg, and decreases with higher doses. Peak plasma concentrations of the unchanged active substance are reached 8 to 12 hours after a single oral dose. Administering the drug with food increases bioavailability in terms of AUC (area under the concentration-time curve) by about 60% and tends to accelerate the absorption rate. After administration of a single oral dose of 200 mg clofazimine with breakfast, mean (\pm SD) peak plasma concentrations of 0.41 (\pm 0.14) microgram per mL (861 (\pm 289) pmol/g) were measured in healthy volunteers. When clofazimine is taken on an empty stomach, the peak plasma concentration was approximately 20% lower.

After repeated administration of clofazimine to leprosy patients in daily doses of 50 mg and 100 mg, mean morning trough concentrations of 0.27 and 0.43 microgram per mL (580 pmol/g and 910 pmol/g), respectively, were measured after 42 consecutive days. Steady-state concentrations were not reached within this time period.

Distribution

Clofazimine is strongly lipophilic and accumulates mainly in fatty tissue and in macrophages of the reticuloendothelial system. After long-term treatment, clofazimine has been detected in the following organs and tissues and body fluids: subcutaneous fat, mesenteric lymph nodes, bile and gall bladder, adrenals, spleen, small intestine, liver, muscle tissue, bones, and skin. Clofazimine does not appear to cross the intact blood-brain barrier.

Clofazimine crosses the placenta and passes into the breast milk in sufficient quantities to colour the milk.

Biotransformation/Metabolism

Information on the metabolism of clofazimine is limited. Three metabolites, of which two are glucuronides, have been identified in urine.

Elimination

Clofazimine is eliminated slowly from the plasma. The mean elimination half-life of the unchanged substance following a single dose of 200 mg in healthy volunteers was 10.6 (\pm 4.0) days. After repeated administration of 50 mg and 100 mg daily to leprosy patients, the elimination half-life was about 25 days.

Unchanged clofazimine is excreted via the bile mainly in the faeces. Within 3 days on average, 35% of the dose is recovered. No more than 0.4% of the dose is found in the urine as unchanged clofazimine after 24 hours. The urinary metabolites account for about 0.6% of the daily dose.

Special populations

No data is available on the effects of renal or hepatic dysfunction, or of age on the pharmacokinetics of clofazimine.

Clinical studies

Not applicable.

Non clinical safety data

Long-term carcinogenicity studies in animals have not been conducted with clofazimine. No mutagenic activity was detected in the Ames test. There is some evidence for a clastogenic potential in mice. No primary teratogenic effect was observed in the offspring of rats and rabbits treated during pregnancy with clofazimine in doses of up to 50 mg/kg/day and 15 mg/kg/day, respectively (25 and 8 times the usual human dose). However, with doses 12 to 25 times those given to humans, there was evidence of foetotoxicity in mice at doses of 50 mg/kg/day, and foetal skull ossification was somewhat delayed.

Pharmaceutical information

Incompatibilities

None known.

Shelf life

Not for use after the date marked "EXP" on the pack.

Special precautions for storage

- Protect from moisture, store below 25°C.
- Lamprene must be kept out of the reach and sight of children.

Instructions for use and handling

No special requirements.

Special precautions for disposal

No special requirements.

Medicine classification

Prescription Medicine

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