

Drug Regulatory Affairs

LAMPRENE[®]

(clofazimine)

50 or 100 mg capsules, soft

International Package Leaflet

Lamprene®

Clofazimine

COMPOSITION AND PHARMACEUTICAL FORM

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

For excipients, see section EXCIPIENTS.

Certain dosage strengths may not be available in all countries.

INDICATIONS

Lamprene, employed in combination with Rimactane® (rifampicin) and dapsone, serves as treatment for multibacillary (MB) forms of leprosy, with positive skin smear (lepromatous (LL), borderline lepromatous (BL), mid-borderline (BB) leprosy) or all cases clinically diagnosed as multibacillary with more than 5 skin lesions, as well as 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 (LL, BL, BB)

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

Children <10 years: The dose should be adjusted appropriately, for example, Lamprene 100 mg once a month under supervision + 50 mg twice a week as self-medication + Rimactane® (rifampicin) 300 mg once a month under supervision + dapsone 25 mg once a day as self-medication.

This triple combination should be given for 12 months.

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 200-300 mg daily, given under medical supervision. These high daily doses must not be given for longer than 3 months.

Method of Administration

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

CONTRAINDICATIONS

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

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Lamprene should never be used alone for the treatment of leprosy. Multidrug therapy is necessary to prevent the emergence of drug resistance.

Warnings

After prolonged administration in high doses, clofazimine may accumulate in tissue, e.g. the wall of the small bowel, and precipitate. Enteropathy may develop if crystals are deposited in the lamina propria of the jejunal mucosa and the mesenteric lymph nodes, sometimes leading 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

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

Daily doses of >100 mg Lamprene should be given for as short a time as possible (<3 months) and only under close medical supervision.

Physicians should be aware that skin discoloration due to Lamprene 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.

INTERACTIONS

Dapsone

Lamprene 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 Lamprene have not been confirmed. If leprosy-associated inflammatory reactions develop in patients being treated with dapsone and Lamprene, 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 LACTATION

Pregnancy

No mutagenic activity was detected in the Ames test and in cytogenic tests in patients treated with Lamprene. No teratogenic effect was observed in rabbits or rats given clofazimine doses 8 and 25 times the usual human dose, respectively. However, with doses 12 to 25 times those given to humans, retardation of fetal skull ossification and fetotoxicity were observed in mice.

Experience with Lamprene in pregnancy is limited. Clofazimine crosses the placenta, and skin discoloration in neonates has been observed. Lamprene should be used during pregnancy only if the potential benefit justifies the risk to the fetus. Since leprosy is exacerbated during pregnancy, the WHO recommends that treatment with Lamprene should be continued during pregnancy.

Lactation

Clofazimine passes into the breast milk, and skin discoloration may occur in the infant. Lamprene should be administered to a breast-feeding woman only if clearly indicated.

EFFECTS ON ABILITY TO DRIVE AND USE 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.

UNDESIRABLE EFFECTS

Adverse reactions (Table 1) are ranked in descending order of frequency, as follow: 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 1

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 leprous 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 Lamprene.

OVERDOSE

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

PHARMACODYNAMICS

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 dapson 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 dapson. 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.

PHARMACOKINETICS

Absorption

Clofazimine is absorbed relatively slowly. Bioavailability of clofazimine from the micronised suspension in an oil-wax base 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 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 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, but never in the brain. 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

Information on the metabolism of clofazimine is limited. Three metabolites, two 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.

Characteristics in patients

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

PRECLINICAL SAFETY DATA

Long-term carcinogenicity studies in animals have not been conducted with clofazimine. No mutagenic activity was detected in the Ames test. 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. However, there was evidence of fetotoxicity in mice at doses of 50 mg/kg/day, and fetal skull ossification was somewhat delayed.

EXCIPIENTS

Butylated hydroxytoluene (E 321); sodium salt of ethyl hydroxybenzoate (E215); sodium salt of propyl hydroxybenzoate (E 217); p-methoxy acetophenone; propylene glycol; rapeseed oil; soybean lecithin; hydrogenated soybean oil; partially hydrogenated vegetable oils; beeswax; gelatin; glycerol 85%; citric acid anhydrous; ethylvanillin; black iron oxide, red iron oxide (E172).

INCOMPATIBILITIES

None known.

STORAGE

Protect from moisture, store below 25°C.

Lamprene should not be used after the date marked "EXP" on the pack.

INSTRUCTIONS FOR USE AND HANDLING

Note: Lamprene should be kept out of the reach and sight of children.

Manufacturer:

See folding box.

International Package Leaflet

Information issued: June 2005

® = registered trademark

Novartis Pharma AG, Basel, Switzerland