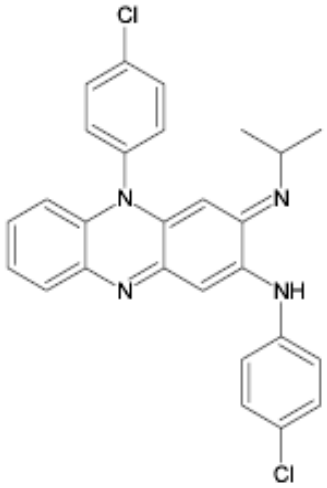
LAMPRENE®
(Clofazimine)

NAME OF THE DRUG

Active ingredient:	Clofazimine
Chemical name:	3-(p-Chloro-anilino)-10-(p-chlorophenyl)-2,10-dihydro-2-(isopropylimino)-phenazine
CAS number:	2030-63-9
Molecular weight:	473.40
Molecular formula:	$C_{27}H_{22}Cl_2N_4$
Chemical structure:	

DESCRIPTION

Clofazimine is a reddish brown microcrystalline powder. It is insoluble in water, slightly soluble in alcohol and glycols; soluble in dimethylformamide and macrogol 400.

Each Lamprene capsule contains 50 mg or 100 mg of the antileprosy drug, clofazimine, in an oil-wax base. Each capsule also contains: acetanisole, butylated hydroxytoluene (E321), citric acid monohydrate (E330), propylene glycol, lecithin, beeswax - white, and vegetable oil – hydrogenated. The soft gelatin capsule shell contains: sodium ethyl hydroxybenzoate (E215), ethyl vanillin, gelatin, glycerol (E422), sodium propyl hydroxybenzoate, iron oxide black CI77499 (E172), iron oxide red CI77491 (E172), and rape seed oil.

PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group: Antileprosy drug
ATC Code: J04BA01

Clofazimine exerts in man a bacteriostatic and mildly bactericidal effect on *Mycobacterium leprae* (*M. leprae* , Hansen's bacillus). Since its mechanism of action differs from that of dapsone and rifampicin, no cross-resistance occurs with the latter drugs.

Clofazimine also possesses anti-inflammatory properties.

Pharmacokinetics

Absorption

Clofazimine is absorbed slowly and incompletely. Peak plasma concentrations of the unchanged active substance are reached 8 to 12 hours after a single oral dose given in capsule form. Administering the drug with food increases bioavailability in terms of AUC (area under the concentration-time curve) and tends to accelerate the absorption rate.

The average serum concentrations in leprosy patients treated with 100 mg clofazimine and 300 mg clofazimine daily were 0.7 mcg/mL and 1.0 mcg/mL respectively.

Distribution

Clofazimine is strongly lipophilic and accumulates chiefly in fatty tissue and in the macrophages of the reticulo-endothelial system. Autopsies of patients who had undergone long-term treatment with Lamprene showed that clofazimine was particularly detectable in subcutaneous fat, mesenteric lymph nodes, bile and gall bladder, and in the 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

Metabolism

Information on the metabolism of clofazimine is limited.

Elimination

Clofazimine is retained in the human body for a long time and is eliminated slowly from the plasma. The half-life of Lamprene following repeated oral doses is estimated to be at least 70 days.

Clofazimine is excreted via the bile mainly in the faeces; the amount recovered representing biliary excretion as well as unabsorbed drug.

Pharmacokinetics in special patient groups:

Use in patients with impaired renal or hepatic function: No data are available on the effects of renal or hepatic dysfunction on the pharmacokinetics of clofazimine. See PRECAUTIONS.

Use in elderly patients: No data are available on the effects of age on the pharmacokinetics of clofazimine.

INDICATIONS:

Lamprene, employed in combination with dapsone and rifampicin, serves as treatment for multi-bacillary (MB) forms of leprosy, such as lepromatous (LL), borderline lepromatous (BL), and mid-borderline (BB) leprosy, as well as erythema nodosum leprosum (ENL).

Combined chemotherapy is necessary in order to prevent emergence of resistant strains of *M. leprae.*

CONTRAINDICATIONS

Hypersensitivity to clofazimine or to any of the excipients of Lamprene.

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 (MDT) 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 to DOSAGE AND ADMINISTRATION for Lamprene dosing in patients who develop ENL reactions. Lepra reactions usually respond satisfactorily to standard anti-inflammatory therapy (prednisolone).

Clofazimine has a 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 visceras, 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.

Severe abdominal symptoms have necessitated exploratory laparotomy in some patients receiving Lamprene. Rare reports have included splenic infarction, bowel obstruction and gastro-intestinal bleeding. There have also been reports of death following severe abdominal symptoms.

Daily doses of Lamprene exceeding 100mg should not be administered for longer than 3 months, during which time the patient should be kept under close medical supervision. Please refer to DOSAGE AND ADMINISTRATION. After prolonged administration in high doses, clofazimine may accumulate in tissues (eg. 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 gastro-intestinal symptoms develop during treatment with Lamprene, the dosage should be reduced or the interval between doses increased. In the event of persistent diarrhoea or vomiting, the patient should be hospitalised.

The use of Lamprene in patients with a history of recurrent abdominal pain or diarrhoea or impairment of hepatic or renal function should be avoided, wherever possible.

Physicians should be aware that skin discolouration due to Lamprene may result in depression. Two cases of depression with suicide have been reported. Patients should be warned that Lamprene may cause discolouration of the conjunctiva, lacrimal fluid, sweat, sputum, urine, faeces, nasal secretions, semen, breast milk and reddish to brownish-black discolouration of the skin. Patients should be told that discolouration of the skin, although reversible, may take several months or years to disappear after the end of therapy with Lamprene.

Interactions with Other Medicines

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.

Interaction with anti-retroviral drugs: 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.

Use in Pregnancy - Category C

Lamprene should be prescribed with caution during pregnancy especially in the first 3 months. Due to the long half-life and teratogenic potential of clofazimine, administration of Lamprene should if possible be stopped at least 3 months before intended conception.

The active ingredient of Lamprene crosses the placenta and may cause discolouration of the baby. This is reversible, but recovery may be delayed because of the drug's long serum half-life.

Use in Lactation:

Clofazimine passes into breast milk and skin discolouration 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:

Decreased visual acuity, dizziness, tiredness and headache have been reported during Lamprene therapy. Patients experiencing such adverse reactions should not drive a vehicle or operate machines.

ADVERSE EFFECTS

Adverse drug reactions 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 (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (1/1,100, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (<1/10,000), including isolated reports.

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

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, increase in blood bilirubin, jaundice and increase in AST

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: exfoliative dermatitis

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

Depression was reported to be due to skin discolouration and two suicides were reported. Red to brownish-black discolouration of the skin and leprous lesions, particularly in light-skinned patients, at sites exposed to light. Discolouration of the hair, the conjunctiva, cornea and lacrimal fluid, as well as of sweat, sputum, urine and faeces. This discolouration is reversible on cessation of treatment, although in the case of the skin, it often does not disappear completely until some months after cessation of treatment. The corneal pigmentation (subepithelial corneal brownish pigmented lines) is due to crystal deposits. It is reversible on discontinuation of treatment. Some of the adverse reactions to clofazimine are mainly linked to its uptake by tissue and organs (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION:

Dosage

For the treatment of leprosy, Lamprene should be employed in combination with other anti-leprosy drugs.

Adults (of approx. 60kg body weight): For the treatment of multibacillary leprosy (LL, BL, BB) the WHO (World Health Organisation) recommends the following dosage schedule:

Lamprene: 50 mg once a day as self-medication
AND
300 mg once a month under supervision
Rifampicin: 600 mg once a month under supervision
Dapsone: 100 mg once a day as self-medication
This threefold combination should be administered for at least 2 years and, whenever possible, until such time as the patient's skin smears become negative.

If the patient develops ENL, the treatment with dapsone and rifampicin should be continued as before, whereas the dosage of Lamprene should be raised to not more than 300 mg per day. These high daily doses must not be given for longer than 3 months (see PRECAUTIONS).

Children: Children should receive lower doses adapted to their body weight.

Administration

Capsules for oral administration. The capsules should be taken during meals or together with milk.

OVERDOSAGE:

Acute poisoning with clofazimine has not been described.

Signs and Symptoms:
The following signs and symptoms might be encountered in the presence of acute poisoning: dizziness, headache, nausea, vomiting, gastralgia, diarrhoea, disorders of hepatic and renal function (associated with oliguria or anuria, haematuria, albuminuria, and an increase in blood urea nitrogen), and disturbances in the fluid and electrolyte balance. Prolonged, but reversible, reddish discolouration of the skin and urine can be expected.

Treatment:
No specific data are available on the treatment of overdose with Lamprene.There is no specific antidote.

Telephone the Poisons Information Centre on 131 126 for advice on the management of an overdose.

In conjunction with general measures to eliminate the drug and reduce its absorption, symptomatic treatment may be considered.

PRESENTATION AND STORAGE CONDITIONS

Presentation

- Soft gelatin capsule containing clofazimine 100mg. Imprinted 'GEIGY' in white on one side and 'GM' in white on other side. Containers of 1000.
- Soft gelatin capsule containing clofazimine 50mg. Spherical without imprint. Containers of 100.

Irregular colour of the capsules is due to the active ingredient being present as a microcrystalline suspension in an oil-wax base. The base is dark brown; the suspended particles are reddish-brown. Sedimentation of the suspended material may lead to an irregular (possibly mottled) appearance.

Storage

Store below 25°C. Protect from moisture.

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (S4)

NAME AND ADDRESS OF THE SPONSOR

NOVARTIS Pharmaceuticals Australia Pty Limited
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DATE OF APPROVAL

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