NOVARTIS

Regulatory Affairs

LAMPRENE® (clofazimine)

50 or 100 mg capsules, soft

International Package Leaflet (IPL)

NOTICE

The Novartis Core Data Sheet (CDS) displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

The Novartis CDS contains all relevant information relating to indications, dosage regimen, pharmacology and Core Safety Information which Novartis requires to be listed for the product in all countries where the product is registered.

IPL Creator:	Kiran Kumar Chilipi
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LAMPRENE®

Drugs for the treatment of lepra.

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

Capsules:
Butylated hydroxytoluene; Citric acid, anhydrous; Propylene glycol; Rapeseed oil, refined; Lecithin (E322); Beeswax, yellow; Soybean oil, hydrogenated; Soya-bean oils, partially hydrogenated

Capsule shells:
Ethyl parahydroxybenzoate sodium; Propyl parahydroxybenzoate sodium; Ethylvanillin; Gelatin; Glycerol 85%; Black iron oxide (E172); Red iron oxide (E172); p-Methoxy acetophenone

Pharmaceutical formulations may vary between countries.

INDICATIONS

Leprosy:

Lamprene, used only in combination with rifampicin and dapsone, 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 MB leprosy with more than 5 skin lesions
- for all cases of relapse of previously treated MB leprosy
- for erythema nodosum leprosum (ENL)

Multidrug therapy (MDT) is necessary in order to prevent the emergence of resistant strains of *Mycobacterium leprae*.

Drug resistant Tuberculosis (DR-TB):

Lamprene is indicated, as part of the World Health Organization (WHO) shorter or WHO conventional treatment regimens, for the treatment of pulmonary drug-resistant tuberculosis (DR-TB) including:

- Multidrug-resistant tuberculosis (MDR-TB)
- Rifampicin resistant tuberculosis (RR-TB)
- Extensively drug-resistant TB (XDR-TB)

DOSAGE REGIMEN AND ADMINISTRATION

Multibacillary leprosy:

Lamprene is administered only as part of a multidrug therapy, in combination with dapsone and rifampicin for the treatment of multibacillary leprosy. Multidrug therapy (MDT) is necessary in order to prevent the emergence of resistant strains of *Mycobacterium leprae*.

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

Table-1 MDT dosage

	Dapsone	Rifampicin	Lamprene (clofazimine)
Adults and adolescents (15 years and above)	Days 1-28 100 mg once daily as self-medication	Day 1 only of each cycle* 600 mg under supervision	Day 1 only of each cycle* 300 mg under supervision and Days 2-28 50 mg once daily as self-medication
Children (10 to 14 years)	Days 1-28 50 mg once daily as self-medication	Day 1 only of each cycle* 450 mg under supervision	Day 1 only of each cycle* 150 mg under supervision and Days 2-28 50 mg on alternate days (i.e. day 3, 5, 7, …) as self-medication

This triple combination should be given for 12 months (i.e. *12 consecutive 28-day treatment cycles). An additional 12 months of this triple combination may be necessary for MB patients showing evidence of relapse.

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.

Treatment of children below 10 years of age is possible only if dapsone tablets of 25 mg are commercially available.

Patients with erythema nodosum leprosum (ENL)

Adults and children: If the patient develops ENL, treatment with rifampicin and dapsone should be continued as before, and the dosage of clofazimine increased 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 WARNINGS AND PRECAUTIONS). The dose of clofazimine should be

gradually reduced, first to 100 mg twice daily for 12 weeks and then to 100 mg once daily for a further 12 to 24 weeks.

Drug-resistant tuberculosis (DR-TB)

Dosage:

For the treatment of pulmonary DR-TB as part of the WHO shorter or conventional treatment regimen, Lamprene is administered in adults and children as follows:

Adults and adolescents:

- For adults weighing at least 30 kg, the recommended dosage is 100 mg/day.
- For adults weighing less than 30 kg, the recommended dosage is 50 mg/day.

Children (less than 12 years of age):

- For children weighing at least 30 kg, the recommended dosage is 2-5 mg/kg/day, not exceeding 100 mg/day.
- For children weighing less than 30 kg, the recommended dosage is 2-5 mg/kg/day, not exceeding 50 mg/day. If a dose lower than 50 mg/day is required, the 50 mg dose can be given every other day.

Treatment regimen:

Lamprene is used as part of the WHO recommended conventional treatment regimen (18 to 24 months) for the treatment of pulmonary drug-resistant tuberculosis (MDR-TB/XDR-TB) or as part of the WHO shorter treatment regimen (9-12 Months), only for patients with rifampicin resistant or multi-drug resistant tuberculosis (RR-/MDR-TB).

Lamprene must always be used as part of combination regimen with other effective anti-tuberculosis (anti-TB) drugs. The treatment regimen and duration of treatment should follow the WHO treatment guidelines. It is recommended to refer to the latest WHO treatment guidelines for DR-TB for the current dosage regimen recommendation.

Directly observed therapy (DOT) may be appropriate for DR-TB treatment as per local guidelines.

Dosing in special populations

Patients with concomitant HIV infection:

Information from HIV-positive and immune-compromised leprosy patients and TB indicates that the response to clofazimine, including treatment of leprosy reactions, is not altered, and that no dose adjustments are required in these patients.

Renal impairment

There are no data available in patients with renal impairment. Clofazimine may be used in patients with mild to moderate renal impairment. However, caution should be exercised while administering clofazimine to patients with severe renal impairment.

Hepatic impairment

There are no data available in patients with hepatic impairment. Clofazimine should not be administered to patients with hepatic impairment unless the benefit clearly outweighs the risk (see section CLINICAL PHARMACOLOGY).

Method of administration

Lamprene should be taken with a meal or with a glass of milk to ensure maximum absorption.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Patient adherence

Lamprene should never be used as monotherapy for the treatment of leprosy or DR-TB. Clofazimine must be used in combination with other drugs according to the dosing regimens described in section DOSAGE REGIMEN AND ADMINISTRATION for the treatment of leprosy and DR-TB.

Multidrug therapy is necessary to prevent the emergence of drug resistance. Patients should be informed of the importance of adherence with the prescribed drug regimen in order to prevent drug resistance. Irregularity in administration of medication and poor adherence can lead to delayed and incomplete cure, rendering the patient a source of contamination.

In leprosy patients poor adherence to treatment can ultimately result in the development of disabilities and deformities. Whenever possible, efforts should be made to ensure that non-adhering patients receive adequate assessment, health education and supervised treatment.

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

Lepra reactions

The WHO generally recommends not interrupting MDT during lepra reactions. Please refer to section DOSAGE REGIMEN AND ADMINISTRATION for Lamprene dosing in patients who develop ENL (erythema nodosum leprosum) reactions. Some data indicate a trend towards reduction in the frequency and severity of ENL 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. Lepra reactions usually respond satisfactorily to standard anti-inflammatory therapy (prednisolone).

Accumulation of clofazimine

The deposition of large amounts of clofazimine in the intestinal mucosa causes irritation, leading to gastrointestinal disturbances (e.g. abdominal pain [sometimes intermittent], nausea, vomiting and diarrhea) usually with mild forms, but sometimes with more severe clinical manifestations. Clofazimine has heterogeneous distribution throughout the body and a slow elimination rate, accumulating mainly in fatty tissue, the reticuloendothelial system (macrophages, histiocytes and spleen), and the 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. After prolonged administration in high doses, clofazimine may accumulate in various organs, body fluids and tissues as crystals. Among the viscera, the jejunum has the highest drug deposition, closely followed by the spleen. If crystals are deposited in the mesenteric lymph nodes and/or histiocytes at the lamina propria of the jejunal mucosa, this may lead to intestinal obstruction. Fatalities have been reported following gastrointestinal side effects. 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 diarrhea or vomiting, the patient should be hospitalized.

Skin discoloration

Physicians should be aware that skin discoloration due to clofazimine may result in depression (isolated 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, feces, nasal secretions, semen and 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.

Torsades de pointes and QT prolongation

Cases of Torsades de Pointes with QT prolongation have been reported in patients receiving clofazimine at doses higher than usually recommended or in combination with QT-prolonging medications, and therefore caution is required in the treatment of these patients (see section INTERACTIONS). Patients receiving clofazimine at doses higher than usually recommended or in combination with QT-prolonging medications should have regular ECGs performed to monitor for QT prolongation and cardiac rhythm disturbances.

Interactions

As clofazimine is predicted to be a moderate to strong inhibitor of CYP3A (CYP3A4 and CYP3A5) substrates, caution should be exercised while co-administering clofazimine with drugs which are CYP3A substrates (see Section INTERACTIONS).

Driving and using machines

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

ADVERSE DRUG REACTIONS

Summary of the safety profile

The safety profile of Lamprene is similar when used in leprosy and DR-TB.

Tabulated summary of 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 (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports.*

Table-2 Summary of adverse drug reactions

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 reduced, dry eye, 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, decreased appetite
	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 has been reported due to skin discoloration, and drug related isolated cases of suicides have been 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 or years to disappear after the end of treatment. Corneal pigmentation (subepithelial corneal brownish pigmented lines) is due to crystal deposits. It is reversible on discontinuation of Lamprene. Some of the adverse reactions to clofazimine are mainly linked to its uptake by tissue and organs (see section WARNINGS AND PRECAUTIONS).

INTERACTIONS

Dapsone

Lamprene appears 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. Limited 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 the peak serum concentration to be reached and prolonging the elimination half-life. Total exposure (AUC) of rifampicin 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 QT prolonging drugs

Cases of Torsades de Pointes with QT prolongation have been reported in patients receiving clofazimine in combination with QT prolonging medications. Caution is recommended when

clofazimine is administered with other drugs (e.g: bedaquiline, fluoroquinolones) with known QT interval prolonging potential (see Section WARNINGS AND PRECAUTIONS).

Effects of clofazimine on CYP3A (CYP3A4 and CYP3A5) substrates:

No clinical drug interaction studies have been performed with CYP3A substrates.

Clofazimine inhibits the CYP3A enzyme *in vitro*. Based on PBPK modeling results, clofazimine is predicted to be a moderate to strong CYP3A inhibitor. Hence, caution should be exercised with the concomitant administration of clofazimine and CYP3A substrates (e.g.: simeprevir, tipranavir, delamanid, lercanidipine, simvastatin, lovastatin).

Effects of other drugs on clofazimine:

In a healthy volunteer study of a combination regimen including clofazimine, cycloserine, ethionamide, para-aminosalicyclic acid, and pyridoxine, the C_{max} and T_{max} values of clofazimine were similar to those reported in other studies where clofazimine was administered alone, suggesting no major effects of these drugs on the pharmacokinetics of clofazimine.

In patients with pulmonary TB, where clofazimine was dosed alone and in combination with bedaquiline, pyrazinamide and pretomanid, the C_{max} and AUC values of clofazimine were similar between the groups suggesting no major effects of these drugs on the pharmacokinetics of clofazimine.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

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

Experience with Lamprene in pregnancy is limited. Clofazimine crosses the placenta, and skin discoloration has been observed in neonates.

Animal studies revealed no evidence of teratogenicity but adverse effects on the fetus were noted at high dosages.

Animal data

No teratogenic effect was observed in the offspring of rodents and rabbits treated during pregnancy with clofazimine at oral doses of up to 50 mg/kg/day and 15 mg/kg/day, respectively. In the mouse, there were signs of fetotoxicity (e.g. retardation of fetal skull ossification) at a dose (50 mg/kg/day) considered sufficiently in excess of the human dose.

Lactation

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

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

Females and males of reproductive potential

Infertility

There was some evidence of impaired fertility in one study in female rats receiving clofazimine 50 mg/kg/day (see section NON-CLINICAL SAFETY DATA).

Overdosage

Please refer to the Torsades de pointes and QT prolongation subsection in the WARNINGS AND PRECAUTIONS section.

No specific data are available on the treatment of overdose with Lamprene. In cases of acute overdose, symptomatic treatment may be given as required.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

Lamprene is thought to exert its anti-mycobacterial effect through multiple mechanisms.

The primary mechanism of action for the antimicrobial activity of clofazimine can be postulated through its membrane-directed activity, including the bacterial respiratory chain and ion transporters. Intracellular redox cycling, involving oxidation of reduced clofazimine, leads to the generation of antimicrobial reactive oxygen species (ROS), superoxide-hydrogen peroxide (H_2O_2).

Secondly, interaction of clofazimine with membrane phospholipids results in the generation of antimicrobial lysophospholipids, which promote membrane dysfunction, resulting in interference with K^+ uptake. Both mechanisms result in interference with cellular energy metabolism by disrupting ATP production.

The third proposed mechanism of action is binding preferentially to mycobacterial deoxyribonucleic acid (DNA) with particular affinity to guanine bases and inhibiting mycobacterial replication and growth.

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

Anti-inflammatory activity of clofazimine is primarily through inhibition of T lymphocyte activation and proliferation. Clofazimine may indirectly interfere with the proliferation of T cells by promoting the release of ROS and E-series prostaglandins (PGs), especially PGE2 from neutrophils and monocytes.

Clofazimine may also exert anti-mycobacterial activity by its effect on tissue macrophages, which are the main targets of infection as well as immune response in TB. Clofazimine has a tendency to concentrate selectively in cells of the reticuloendothelial system, which are the main targets of mycobacterial infection, and this enables it to deliver its action at the intended target. This selective accumulation of clofazimine in macrophages is also believed be involved in the drug's anti-inflammatory properties.

Clofazimine has shown apoptosis inducing properties in activated macrophages, which may be responsible for both anti-inflammatory as well as antibacterial actions of the drug. Clofazimine has been shown to inhibit MtSerB2, a phosphatase produced by *M. tuberculosis* that is believed to help the pathogen to evade the host's immune response. The immunosuppressive properties of clofazimine may be either detrimental of beneficial in TB therapy. The immunosuppressive activity may contribute explain to the lack of early bactericidal activity, but later may contribute to the eradication of slow growing persistent pathogens.

Pharmacodynamic properties (PD)

Leprosy:

The major role of the dapsone-clofazimine component of the MDT regimen for MB leprosy is to ensure elimination of spontaneously occurring rifampicin-resistant mutants (estimated to be less than or equal to 10^4 organisms in an untreated patient with lepromatous leprosy). Daily treatment with dapsone-clofazimine alone for 3 months killed more than 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.

In humans, clofazimine exerts a bacteriostatic and weak bactericidal effect on *Mycobacterium leprae* (*M. leprae*, Hansen's bacillus). Clofazimine appears to bind preferentially to mycobacterial DNA and inhibit mycobacterial replication and growth.

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.

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.

DR-TB

The MIC of clofazimine against drug susceptible as well as single drug-resistant, multidrug-resistant and extensively drug resistant TB strains ranges from <0.0625 μg/mL to > 1 μg/mL. The majority [84.7% (95% CI: 69.5%, 93.1%)] of the tested strains have a reported MIC value of ≤ 0.5 μg/mL for clofazimine.

Clofazimine does not show cross-resistance with isoniazid or rifampin. *In vitro* resistance to clofazimine in *mycobacterium tuberculosis* has been mapped to mutations in the transcriptional

regulator Rv0678 which results in the upregulation of MmpS5-MmpL5, an efflux pump. These mutants show cross-resistance to bedaquiline. Two additional mutations (Rv1979c and Rv2535c) have also been associated with clofazimine resistance *in vitro*; however, the mechanism and clinical relevance of these mutations is yet to be determined

Pharmacokinetic properties (PK)

Absorption

Clofazimine is absorbed relatively slowly. Bioavailability of clofazimine from the micronized suspension in an oil-wax base (such as that of Lamprene capsules) is up to 70% after a dose of 100 mg, and decreases with higher doses. The time to reach peak plasma concentration (median time) of clofazimine decreases from 12 to 8 hours under fed conditions relative to the fasted state. Administering the drug with food increases the 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 a morning meal, mean (±SD) peak plasma concentrations of 0.41 (±0.14) micrograms per mL (861 (±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 trough concentrations of 0.27 and 0.43 micrograms / 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. The accumulation ratios after 50 and 100 mg daily doses of clofazimine on day 42 were 9.88 and 11.61, respectively. The estimated time to reach steady-state plasma concentration after a 50 mg daily dose in leprosy patients was 70 days.

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, 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 cause discoloration of the milk.

Clofazimine bound to the alpha- and beta-lipoproteins in serum, particularly the beta-lipoproteins, and the binding was saturable at approximately 10 microgram/mL (21141 pmol/g) concentrations. Binding to gamma-globulin and albumin was negligible.

Biotransformation/Metabolism

Information on the metabolism of clofazimine is limited. Three metabolites, two of which 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 (±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 feces. Within 3 days on average, 35% of the dose is recovered in feces. No more than 0.4% of the dose is found in the urine as unchanged clofazimine after 24 hours. 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

No recent clinical trials have been conducted by Novartis with Lamprene

NON-CLINICAL SAFETY DATA

Carcinogenicity and mutagenicity

Long-term carcinogenicity studies in animals have not been conducted with clofazimine. No mutagenic activity was detected in the Ames test but there is some evidence of clastogenic potential in mice.

Reproductive toxicity

For reproductive toxicity, see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

There was some evidence of impaired fertility in one study in female rats receiving clofazimine 50 mg/kg/day (from 9 weeks before mating until weaning); the number of offspring was reduced and there was a lower proportion of implantations. Lower doses (5 and 25 mg/kg/day) had no such effects.

Incompatibilities

None known.

Storage

See folding box.

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

Lamprene must be kept out of the reach and sight of children.

Manufacturer:

See folding box.

International Package Leaflet

Information issued: May 2018

® = registered trademark

Novartis Pharma AG, Basel, Switzerland