

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LAMPRENE safely and effectively. See full prescribing information for LAMPRENE.

LAMPRENE® (clofazimine) capsules, for oral use

Initial U.S. Approval: 1986

RECENT MAJOR CHANGES

Dosage and Administration (2)	7/2016
Contraindications (4)	7/2016
Warnings and Precautions (5)	7/2016

INDICATIONS AND USAGE

LAMPRENE is an antimycobacterial indicated for the treatment of lepromatous leprosy, including dapson-resistant lepromatous leprosy and lepromatous leprosy complicated by erythema nodosum leprosum. (1.1)

To prevent the development of drug-resistance, LAMPRENE should be used only as a part of combination therapy for initial treatment of lepromatous leprosy. (1.2)

DOSAGE AND ADMINISTRATION

- For dapson-sensitive lepromatous leprosy, 100 mg daily with meals as a part of a combination regimen for at least 2 years is recommended. (2.1)
- For dapson-resistant lepromatous leprosy, 100 mg daily with meals in combination with one or more other agents for 3 years. (2.1)
- For lepromatous leprosy complicated by erythema nodosum leprosum, 100 mg to 200 mg daily for up to 3 months. Taper dose to 100 mg as quickly as possible. (2.1)

DOSAGE FORMS AND STRENGTHS

50 mg soft gelatin capsules. (3)

CONTRAINDICATIONS

Known hypersensitivity to clofazimine or to any of the excipients of LAMPRENE. (4)

WARNINGS AND PRECAUTIONS

- Abdominal obstruction and other gastrointestinal adverse reactions: LAMPRENE may deposit in intestinal mucosa causing intestinal disturbances, including abdominal obstruction, bleeding, splenic infarction and death. Reduce dose or discontinue LAMPRENE if patient complains of pain in abdomen or other gastrointestinal symptoms. (5.1)
- QT prolongation: QT prolongation and Torsades de Pointes may occur with LAMPRENE. Coadministration with other QT prolonging drugs or with bedaquiline may cause additive QT prolongation. Monitor ECGs and discontinue LAMPRENE if significant ventricular arrhythmia or QTcF interval greater than or equal to 500 ms develop. (5.2)
- Skin and body fluid discoloration and other skin reactions: Advise patients that skin and body fluid discoloration frequently occur with use of LAMPRENE. (5.3)
- Depression and suicide due to skin discoloration. Monitor patients for psychological effects of skin discoloration. (5.4)

ADVERSE REACTIONS

Most common adverse reactions reported in 40% to 50% of patients are skin and body fluid discoloration, abdominal and epigastric pain, diarrhea, nausea, vomiting, gastrointestinal intolerance. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Human Immunodeficiency Virus (HIV) Patients: No dose adjustment of LAMPRENE is needed for HIV-infected patients (8.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 7/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Lepromatous Leprosy
- 1.2 Usage

2 DOSAGE AND ADMINISTRATION

- 2.1 Dosage
- 2.2 Important Pre-test Prior to Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Abdominal Obstruction and Other Gastrointestinal Adverse Reactions
- 5.2 QT prolongation
- 5.3 Skin and Body Fluid Discoloration and Other Skin Reactions
- 5.4 Psychological Effects of Skin Discoloration

6 ADVERSE REACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy

- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Patients with HIV Co-infection

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Lepromatous Leprosy

LAMPRENE is indicated in combination with other antileprosy drugs for the treatment of lepromatous leprosy, including dapsone-resistant lepromatous leprosy, and lepromatous leprosy complicated by erythema nodosum leprosum.

1.2 Usage

To prevent the development of drug-resistance, LAMPRENE should be used only as a part of combination therapy for initial treatment of lepromatous (multibacillary) leprosy [see *Dosage and Administration* (2.1)].

For further guidance on the treatment of leprosy, contact the National Hansen's Disease Clinical Center, Baton Rouge, Louisiana (LA) at (1-800-642-2477) or <http://www.hrsa.gov/hansensdisease/clinicalcenter.html>.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

- **Dapsone-sensitive Lepromatous (multibacillary) Leprosy**

Administer 100 mg LAMPRENE daily with meals in combination with two other antileprosy drugs for at least 2 years and if possible, until negative skin smears are obtained, followed by monotherapy with an appropriate antileprosy drug.

- **Dapsone-resistant Lepromatous Leprosy**

Administer 100 mg LAMPRENE daily with meals in combination with one or more other antileprosy drugs for 3 years, followed by monotherapy with 100 mg of LAMPRENE daily.

- **Lepromatous Leprosy complicated by Erythema Nodosum Leprosum Reactions**

Administer LAMPRENE at 100 mg to 200 mg daily, in conjunction with baseline antileprosy treatment and steroids as clinically indicated. If LAMPRENE is administered at 200 mg dose, taper to 100 mg as soon as possible after the erythema nodosum reaction is controlled. Doses of LAMPRENE of more than 100 mg daily should be given for as short a period as possible and only under close medical supervision [see *Warnings and Precautions* (5.1)].

2.2 Important Pre-test Prior to Administration

Sexually-active females of reproductive potential should have a pregnancy test prior to LAMPRENE administration [see *Use in Specific Populations* (8.3)].

3 DOSAGE FORMS AND STRENGTHS

Each LAMPRENE capsule contains 50 mg clofazimine in a soft gelatin capsule. The capsules are brown and spherical.

4 CONTRAINDICATIONS

LAMPRENE is contraindicated in patients with known hypersensitivity to clofazimine or any of the excipients of LAMPRENE.

5 WARNINGS AND PRECAUTIONS

5.1 Abdominal Obstruction and Other Gastrointestinal Adverse Reactions

Clofazimine may accumulate in various organs as crystals, including the mesenteric lymph nodes and histiocytes at the lamina propria of the intestinal mucosa, spleen and liver. Deposition in the intestinal mucosa may lead to intestinal obstruction that may necessitate exploratory laparotomy. Splenic infarction, gastrointestinal bleeding, and death have been reported. If a patient complains of pain in the abdomen, nausea, vomiting, or diarrhea, initiate appropriate medical investigations and reduce the daily dose of LAMPRENE, or increase the dosing interval or discontinue the drug. Doses of LAMPRENE of more than 100 mg daily should be given for as short a period as possible (less than 3 months) and only under close medical supervision.

5.2 QT prolongation

Cases of Torsades de Pointes with QT prolongation have been reported in patients receiving dosage regimens containing higher than 100 mg daily dose of LAMPRENE or in combination with QT prolonging medications. For QT prolongation

and Torsades de Pointes cases, the patient must remain under medical surveillance. In all these patients, monitor electrocardiograms (ECGs) for QT prolongation and cardiac rhythm disturbances [see *Dosage and Administration* (2.1)].

QT prolongation has also been reported in patients who were receiving LAMPRENE with bedaquiline at the recommended dosage regimen for each drug. Monitor ECGs if LAMPRENE is coadministered to patients receiving bedaquiline, and discontinue LAMPRENE if clinically significant ventricular arrhythmia is noted or if the QTcF interval is 500 ms or greater. If syncope occurs, obtain an ECG to detect QT prolongation.

5.3 Skin and Body Fluid Discoloration and Other Skin Reactions

LAMPRENE causes orange-pink to brownish-black discoloration of the skin, as well as discoloration of the conjunctivae, tears, sweat, sputum, urine and feces in 75-100% of patients. Advise patients that skin discoloration is likely to occur and that it may take several months or years to reverse after the conclusion of therapy.

Other skin reactions associated with LAMPRENE therapy include ichthyosis, dry skin and pruritus.

5.4 Psychological Effects of Skin Discoloration

Skin discoloration due to LAMPRENE therapy has been reported to result in depression and suicide. Advise patients regarding skin discoloration and monitor for depression or suicidal ideation during LAMPRENE therapy.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Abdominal Obstruction and Gastrointestinal Adverse Reactions [see *Warnings and Precautions* (5.1)]
- QT Prolongation [see *Warnings and Precautions* (5.2)]
- Skin and Body Fluid Discoloration and Other Skin Reactions [see *Warnings and Precautions* (5.3)]
- Psychological Effects of Skin Discoloration [see *Warnings and Precautions* (5.4)]

The following adverse reactions associated with the use of LAMPRENE were identified. Because these adverse reactions are reported from different studies, these adverse reactions cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions Occurring In More Than 1% of Patients

Skin: Pigmentation from pink to brownish-black in 75% to 100% of the patients within a few weeks of treatment; ichthyosis and dryness (8% to 28%); rash and pruritus (1% to 5%).

Gastrointestinal: Abdominal and epigastric pain, diarrhea, nausea, vomiting, gastrointestinal intolerance (40%- to 50%).

Ocular: Conjunctival and corneal pigmentation due to clofazimine crystal deposits; dryness; burning; itching; irritation.

Other: Discoloration of urine, feces, sputum, sweat; elevated blood sugar; elevated erythrocyte sedimentation rate (ESR).

Adverse Reactions Occurring In Less Than 1% of Patients

Skin: Phototoxicity, erythroderma, acneiform eruptions, monilial cheilosis.

Gastrointestinal: Bowel obstruction, gastrointestinal bleeding, anorexia, constipation, weight loss, hepatitis, jaundice, eosinophilic enteritis, enlarged liver.

Ocular: Diminished vision, maculopathy (bull's eye retinopathy).

Nervous: Dizziness, drowsiness, fatigue, headache, giddiness, neuralgia, taste disorder.

Psychiatric: Depression and suicide secondary to skin discoloration.

Laboratory: Elevated levels of albumin, serum bilirubin, and aspartate aminotransferase (AST); eosinophilia; hypokalemia.

Other: Splenic infarction, thromboembolism, anemia, cystitis, bone pain, edema, fever, lymphadenopathy, vascular pain.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data with LAMPRENE use in pregnant women to inform associated risk. Retardation of fetal skull ossification, increased incidences of abortions and stillbirths, and impaired neonatal survival were observed in mice following prenatal exposure to LAMPRENE at 25 mg/kg, equivalent to the 0.6 times maximum recommended human daily dose (200 mg), based on body surface area comparisons. Advise pregnant women of the potential risk to the fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown; however, in the U.S. general population, the estimated background risk of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

Clinical Considerations

Fetal/neonatal adverse reactions

The skin of infants born to pregnant mothers who had received LAMPRENE during pregnancy is pigmented at birth.

Limited data is available regarding the reversibility of discoloration. Based on previous observations, discoloration gradually faded over the first year.

Data

Human Data

There are no studies of LAMPRENE use in pregnant women. Few cases of clofazimine use during pregnancy have been reported in the literature. These reports indicate that the skin of infants born to women who had received LAMPRENE during pregnancy was deeply pigmented at birth. LAMPRENE should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

Animal Data

Embryofetal toxicity studies were conducted in rats, rabbits and mice. In mice LAMPRENE-induced embryotoxicity and fetotoxicity was evident. Retardation of fetal skull ossification, increased incidences of abortions and stillbirths, and impaired neonatal survival were observed following prenatal exposure to LAMPRENE at 25 mg/kg, equivalent to the 0.6 times maximum recommended human daily dose [MRHD] (200 mg), based on body surface area comparisons. The skin and fatty tissue of offspring became discolored approximately 3 days after birth, which was attributed to the presence of clofazimine in the maternal milk. No developmental effects were observed in rat or rabbits orally administered clofazimine during organogenesis at doses up to 50 mg/kg and 15 mg/kg, (equivalent to about 2.4 and 1.5 times the MRHD of 200 mg based on body surface area) respectively. These animal studies were conducted according to the standards at the time of initial drug approval (1986) and not under current regulatory standards.

8.2 Lactation

Risk summary

LAMPRENE is excreted in human milk. Skin discoloration has been observed in breast fed neonates of mothers receiving clofazimine.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LAMPRENE and any potential adverse effects on the breastfed infant from LAMPRENE or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy testing

Sexually-active females of reproductive potential should have a pregnancy test prior to starting treatment with LAMPRENE.

Contraception

Animal studies have shown LAMPRENE to be harmful to the developing fetus. Advise sexually active females of reproductive potential to use effective contraception (methods that result in less than 1 % pregnancy rates) when using LAMPRENE during treatment and for at least 4 months after stopping treatment with LAMPRENE.

Advise males taking LAMPRENE to use a condom during intercourse while on treatment and for at least 4 months after stopping treatment with LAMPRENE.

Infertility

Impaired female fertility (reduced number of offspring and lower proportion of implantations) was observed in one study in rats receiving LAMPRENE [see *Nonclinical Toxicology (13.1)*]. There are no non-clinical data on male fertility.

8.4 Pediatric Use

Safety and effectiveness of LAMPRENE in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of LAMPRENE did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Patients with HIV Co-infection

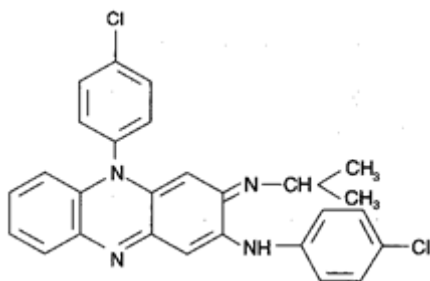
Response to treatment, including treatment of erythema nodosum leprosum reactions, is not altered in HIV-positive and immunocompromised leprosy patients. Dose adjustments of LAMPRENE are not required in these patients.

10 OVERDOSAGE

No specific data are available on the treatment of overdosage with LAMPRENE. However, in case of overdose, the stomach should be emptied by inducing vomiting or by gastric lavage, and supportive symptomatic treatment should be employed.

11 DESCRIPTION

LAMPRENE (clofazimine) is an antimycobacterial available as soft gelatin capsules for oral administration. Each capsule contains 50 mg of micronized clofazimine suspended in an oil-wax base. Clofazimine is a substituted iminophenazine bright-red dye. Its chemical name is 3-(*p*-chloroanilino)-10-(*p*-chlorophenyl)-2, 10-dihydro-2-isopropyliminophenazine, and its structural formula is



Clofazimine is a reddish-brown powder. It is readily soluble in benzene; soluble in chloroform; poorly soluble in acetone and in ethyl acetate; sparingly soluble in methanol and in ethanol; and virtually insoluble in water. Its molecular weight is 473.4. Its molecular formula is $C_{27}H_{22}Cl_2N_4$.

Inactive Ingredients in Capsules: Beeswax, butylated hydroxytoluene, citric acid, ethyl vanillin, gelatin, glycerin, iron oxide, lecithin, *p*-methoxy acetophenone, parabens, plant oils, propylene glycol.

Capsule Shells Contain: ethyl parahydroxybenzoate sodium, propyl parahydroxybenzoate sodium, ethylvanillin, gelatin, glycerol 85%, black iron oxide, red iron oxide, *p*-methoxy acetophenone.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

LAMPRENE is an antimycobacterial drug [see *Microbiology (12.4)*].

12.3 Pharmacokinetics

Absorption

Clofazimine has a variable absorption rate in leprosy patients, ranging from 45% to 62% after oral administration of LAMPRENE. The average serum concentrations of clofazimine in leprosy patients treated with LAMPRENE 100 mg and 300 mg daily were 0.7 mcg/mL and 1 mcg/mL, respectively.

Time to reach peak plasma concentration (median T_{max}) of clofazimine decreases from 12 hours to 8 hours under fed conditions relative to the fasted state.

Distribution

Clofazimine is highly lipophilic and tends to be deposited predominantly in fatty tissue and in cells of the reticuloendothelial system. It is taken up by macrophages throughout the body. In autopsies performed on leprosy patients who had received LAMPRENE, clofazimine crystals were found predominantly in the mesenteric lymph nodes, adrenals, subcutaneous fat, liver, bile, gall bladder, spleen, small intestine, muscles, bones, and skin.

Clofazimine is bound to alpha- and beta-lipoproteins in serum, particularly the beta- lipoproteins, and the binding was saturable at plasma concentrations of approximately 10 mcg/mL. Binding to gamma-globulin and albumin was negligible.

Metabolism

Three clofazimine metabolites were found in urine following repeated oral doses of LAMPRENE. Information on the metabolism of clofazimine is limited.

Elimination

After ingestion of a single 300 mg dose of LAMPRENE, elimination of unchanged clofazimine and its metabolites in a 24-hour urine collection was negligible. Part of the ingested drug recovered from the feces may represent excretion via the bile. A small amount is also eliminated in the sputum, sebum, and sweat. The elimination half-life of clofazimine following repeated oral doses of 50 or 100 mg LAMPRENE in leprosy patients was highly variable with estimates ranging from 6.5 to 160 days. The overall mean half-life of clofazimine in these leprosy patients was approximately 25 days.

12.4 Microbiology

Mechanism of Action

Clofazimine exerts a slow bactericidal effect on *Mycobacterium leprae* (Hansen's bacillus). Clofazimine inhibits mycobacterial growth and binds preferentially to mycobacterial DNA. Clofazimine also exerts anti-inflammatory properties in treating erythema nodosum leprosum reactions. However, its precise mechanisms of action are unknown.

The mechanism of action for the antimycobacterial 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. 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.

Measurement of the minimum inhibitory concentration (MIC) of clofazimine against leprosy bacilli *in vitro* is not yet feasible.

Cross-Resistance

Clofazimine does not show cross-resistance with dapsone or rifampin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term carcinogenicity studies in animals have not been conducted with LAMPRENE. Results of mutagenicity studies (Ames test) were negative. There is some evidence of clastogenic potential in mice.

Impaired female fertility (reduced number of offspring and lower proportion of implantations) was observed in one study in rats receiving LAMPRENE (from 9 weeks before mating until weaning) at 50 mg/kg/day, equivalent to about 2.4 times the maximum recommended clinical dose. No non-clinical data on male fertility are available.

16 HOW SUPPLIED/STORAGE AND HANDLING

How supplied

Soft Gelatin Capsules 50 mg–brown, spherical

Bottles of 100.....NDC 0028-0108-01

Storage and handling

Do not store above 25°C (77°F). Protect from moisture.

Dispense in tight container (USP).

17 PATIENT COUNSELING INFORMATION

Information for Patients

- Inform patients to take LAMPRENE with meals.
- Inform patients to report abdominal pain or other gastrointestinal symptoms, such as nausea or vomiting, to their healthcare provider.
- Inform patients that LAMPRENE frequently causes a red to brownish-black discoloration of the skin as well as discoloration of the conjunctivae, tears, sweat, sputum, urine, and feces. Advise patients that skin discoloration may take several months or years to resolve after the conclusion of therapy with LAMPRENE.
- Inform patients that skin discoloration may result in psychological effects and advise them to report any symptoms of depression or suicidal ideation.
- Advise females of reproductive potential to use effective contraception while taking LAMPRENE and for at least 4 months after stopping treatment with LAMPRENE. It is also recommended that they have a pregnancy test prior to starting treatment with LAMPRENE.
- Advise males taking LAMPRENE to use a condom during intercourse while taking LAMPRENE and for at least 4 months after stopping treatment.
- Inform patients of the importance of compliance with the prescribed drug regimen in order to prevent drug resistance. Irregularity in administration of medication and poor compliance can lead to delayed and incomplete cure, and could result in infecting other people. Poor compliance can result in disease progression and ultimately result in the development of disabilities and deformities. Whenever possible, ensure that non-compliant patients receive adequate assessment, health education and supervised treatment.
- Instruct patients on the recognition of signs and symptoms of inflammatory reactions and relapses during and following completion of treatment, and instruct them regarding the importance of immediately reporting the earliest manifestations of these signs to their healthcare provider.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

© Novartis

T2016-56