These records are from CDER's historical file of information previously disclosed under the Freedom of Information Act (FOIA) for this drug approval and are being posted as is. They have not been previously posted on Drugs@FDA because of the quality (e.g., readability) of some of the records. The documents were redacted before amendments to FOIA required that the volume of redacted information be identified and/or the FOIA exemption be cited. These are the best available copies.

N19500

APRVL

LTR

NDA 19-500

Ms. Rosemarie Rudin
Ciba-Geigy
Summit, New Jersey 07901

Dear Ms. Rudin:

Reference is made to your New Drug Application (NDA) dated June 28, 1985 pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamprene (clofazimine) Capsules.

We also acknowledge receipt of your additional communications dated November 17 and December 2, 1986.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted draft labeling. Accordingly, the application, with the labeling revisions described below, is approved effective as of the date of this letter.

The labeling revisions are as follows:

The last three paragraphs in the Indications section should be deleted.

These revisions are terms of the NDA approval.

Please submit twelve copies of the revised final printed labeling (FPL) when it is available. This submission should be designated for administrative purposes as "FPL Supplement" to the approved NDA 19-500. Approval of the supplement by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of this drug product become available, further revision of that labeling may be required.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

for J Bilstad 12/15/86

Elaine C. Esber, M.D.
Director
Office of Biologics Research and Review
Center for Drugs and Biologics

cc: NWK-DO
ORIG. NDA 19-500
HFN-82 Additional revisions made 12/10/86
HFN-710
HFN-220 ET 12/12/86
HFN-815
HFN-815/CSO/RLinkous/11/13/86/sdj/11/14/86/12/3/86
HFN-815/MO Dr. Stanley not here
HFN-815/CHEM ARC 12/12/86
HFN-815/PHARM [illegible] 12/5/86
R/D init. by: ETabor/11/25/86/12/5/86
F/T: 12/5/86

APPROVED 0542u R Linkous 12/5/86

AE

LETTER

OCT 31 1986

NDA 19-500

Ms. Rosemarie Rudin
Ciba-Geigy
Summit, New Jersey 07901

Dear Ms. Rudin:

Reference is made to your New Drug Application (NDA) dated June 28, 1985 submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Lamprene (clofazamine) Capsules.

We also acknowledge your June 27, 1986 amendment containing revised labeling which incorporated changes discussed at the June 23, 1986 meeting.

We have completed our review of this application and it is approvable. Before the application may be approved, however, the following comments and questions must be addressed and revisions must be made in the labeling where specified:

1. All literature references should be deleted.

2. Description section: delete the word "principal" from the first sentence.

3. Clinical Pharmacology section, Pharmacokinetics subsection

   a. The sources of data used to write this subsection should be identified.

   b. If drug absorption following oral administration ranges from 45 to 62%, then fecal elimination should be, at a minimum, in the range of 38 to 55%. If some absorbed drug is excreted via the bile into the gastrointestinal tract and is not reabsorbed, or absorbed drug passes back through the intestinal wall into the lumen, then fecal elimination should be even higher. This does not appear to be consistent with the statement in this subsection that fecal excretion in some cases amounts to as much as 35% of an oral dose in 24 hours. If significant amounts are excreted after 24 hours, then the reference to 35% excretion in 24 hours does not appear to be meaningful and should be deleted. Please clarify.

4. Clinical Pharmacology section, Microbiology subsection

   a. The statement is made that it is not possible to determine the minimum inhibiting concentration (MIC) of Lamprene against leprosy bacilli in animals because the drug is not homogeneously distributed in the tissues and because of marked tissue accumulation. Does the lack of homogeneous distribution refer to the distribution among different tissues or within the same tissue? If the former, that does not appear to be an explanation why MICs could not be determined within a specified tissue. Also it is not clear how "marked tissue accumulation" is a reason why tissue MICs cannot be done.

   b. In the last sentence of the first paragraph, insert the word "approximately" before "50 days".

5. The Indications and Usage section should read:

   Lamprene is indicated in the treatment of lepromatous leprosy, including dapsone-resistant lepromatous leprosy and lepromatous leprosy complicated by erythema nodosum leprosum. Lamprene has not been demonstrated to be effective in the treatment of other leprosy-associated inflammatory reactions.

   Combination drug therapy has been recommended for initial treatment of multibacillary leprosy to prevent the development of drug resistance.

6. The Warnings section should read as follows and the first paragraph should be in bold print:

   Severe abdominal symptoms (see below) have necessitated exploratory laparotomies in some patients receiving Lamprene. Rare reports have included splenic infarction, bowel obstruction, and gastrointestinal bleeding. There have also been reports of death following severe abdominal symptoms. Autopsies have revealed crystalline deposits of clofazamine in various tissues including the intestinal mucosa, liver, spleen, and mesenteric lymph nodes.

   Lamprene should be used with caution in patients who have gastrointestinal problems such as abdominal pain and diarrhea. Dosages of Lamprene of more than 100 mg daily should be given for as short a period as possible and only under close medical supervision. If a patient complains of colicky or burning pain in the abdomen, nausea, vomiting, or diarrhea, the dose should be reduced, and if necessary, the interval between doses should be increased, or the drug should be discontinued.

7. In the General subsection of the Precautions section, the existing paragraph should be deleted (because the same wording appears in the Warnings section) and should be replaced with the following:

> Physicians should be aware than skin discoloration due to Lamprene may result in depression. Two suicides have been reported in patients receiving Lamprene.
>
> For skin dryness and ichthyosis, oil can be applied to the skin.

8. The Drug Interactions subsection of the Precautions section should read as follows:

> Although preliminary data suggest that dapsone may inhibit the anti-inflammatory activity of Lamprene, these data have not been confirmed. If leprosy-associated inflammatory reactions develop in patients being treated with dapsone and clofazamine, it is advisable to continue treatment with both drugs if otherwise indicated.

9. In the Carcinogenesis, Mutagenesis, Impairment of Fertility subsection of the Precautions section, the third sentence should read:

> There was some evidence of impaired fertility in one study in rats treated at a dose of 25 times the usual human dose; the number of offspring was reduced and there was a lower proportion of implantations.

10. In the Pregnancy subsection of the Precautions section, the first paragraph should read as follows:

> Lamprene was not teratogenic in laboratory animals at dose levels equivalent to 8 times (rabbit) or 25 times (rat) the usual human daily dose. However, there was evidence of fetotoxicity in the mouse at 12-25 times the human dose; i.e., retardation of fetal skull ossification, increased incidence of abortions and stillbirths, and impaired neonatal survival. The skin and fatty tissue of offspring became discolored approximately 3 days after birth, which was attributed to the presence of Lamprene in the maternal milk.

11. In the Adverse Reactions section, sucsection entitled Adverse Reactions Occurring in Less than 1% of Patients:

    a. Insert "Psychiatric: depression secondary to skin discoloration; two suicides have been reported."

    b. The "Other" subsection should read: "Splenic infarction (see WARNINGS), thromboembolism, arteritis."

12. Dosage and Administration section

a. The second and third paragraphs should read as follows:

> Lamprene preferably should be used in combination with one or more other antileprosy drugs to prevent the emergence of drug resistance.
>
> For the treatment of proven dapsone-resistant leprosy, Lamprene should be given at a dosage of 100 mg daily in combination with one or more other antileprosy drugs for 3 years, followed by monotherapy with 100 mg of Lamprene daily for (duration). Clinical improvement usually can be detected between the first and third months of treatment and usually is clearly evident by the sixth month.

b. The first sentence in the fourth paragraph should read as follows:

> For dapsone-sensitive multibacillary leprosy, combination therapy with two other antileprosy drugs is recommended.

c. The second sentence in the fourth paragraph implies that no therapy is required after negative skin smears are obtained. However, many experts believe that life-long therapy is necessary for lepromatous leprosy. Please clarify.

d. In the third and fourth sentences of the fifth paragraph, "300 mg" should be changed to "200 mg". If you believe the 300 mg dosage is justifiable, please submit data to support it.

e. We recommend that a sixth paragraph be added, if acceptable with the USPHS National Hansen's Disease Center, as follows:

> For advice about combination drug regimens, contact the USPHS National Hansen's Disease Center at Carville, LA (telephone number).

Prior to approval of your NDA we are requesting a safety update report as provided for under 21 CFR 314.50(d)(5)(vi)(B).

Please submit, in duplicate, the advertising copy which you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one copy to the Division of Anti-Infective Drug Products, and the second copy to the Division of Drug Advertising and Labeling, HFN-240, Room 10B-64, 5600 Fishers Lane, Rockville, Maryland 20857. Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-[illegible] for this submission; this form is for routine use, not proposed materials.

Within 10 days after the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Sincerely yours,

10/31/86

for Elaine C. Esber, M.D.
Director
Office of Biologics Research and Review
Center for Drugs and Biologics

cc:
Orig NDA 19-500
HFN-82
HFN-800/JMinor
HFN-200
HFN-815
HFN-815/CSO/RLinkous:bam:7/2/86/1230
HFN-815
HFN-815/Pharm
HFN/Chem
Redraft:JMBilstad:pec:10/31/86:10375
Final:JMbilstad:pec:10/31/86

FPL

# Lamprene®

C86-66 (Rev 12.86)

**clofazimine**

667750

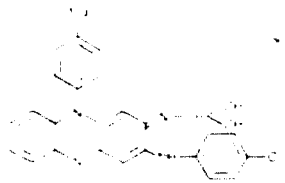
## Capsules

APPROVED 12-15-86

**Prescribing Information**

### DESCRIPTION

Lamprene (clofazimine) is an antileprosy agent available as capsules for oral administration. Each capsule contains 50 mg or 100 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-isopropylimmophenazine, 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.

### CLINICAL PHARMACOLOGY

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

#### Pharmacokinetics

Lamprene has a variable absorption rate in leprosy patients, ranging from 45-62% after oral administration. The average serum concentrations in leprosy patients treated with 100 mg and 300 mg daily were 0.7 µg/ml and 1.0 µg/ml, respectively. After ingestion of a single dose of 300 mg, elimination of unchanged Lamprene and its metabolites in a 24-hour urine collection was negligible. Lamprene is retained in the human body for a long time. The half-life of Lamprene following repeated oral doses is estimated to be at least 70 days. 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.

Lamprene 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, clofazimine crystals were found predominantly in the mesenteric lymph nodes, adrenals, subcutaneous fat, liver, bile, gall bladder, spleen, small intestine, muscles, bones, and skin.

#### Microbiology

Measurement of the minimum inhibitory concentration (MIC) of Lamprene against leprosy bacilli *in vitro* is not yet feasible. In the mouse footpad system, the multiplication of *M. leprae* is inhibited by introducing 0.0001-0.001% Lamprene in the diet. Although bacterial killing may begin shortly after starting the drug, it cannot be measured in biopsy tissues taken from patients for mouse footpad studies until approximately 50 days after the start of therapy.

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

The following *in vitro* data are available, but their clinical significance is unknown. Lamprene has been shown in vitro to inhibit *M. avium* and *M. bovis* at concentrations of approximately 0.1-1.0 µg/ml. The MIC for *M. avium-intracellulare* isolated from patients with acquired immuno-deficiency syndrome (AIDS) ranged from 1.0 to 5.0 µg/ml. With a few exceptions, microorganisms other than mycobacteria are not inhibited by Lamprene.

### INDICATIONS AND USAGE

Lamprene is indicated in the treatment of lepromatous leprosy, including dapsone-resistant lepromatous leprosy and lepromatous leprosy complicated by erythema nodosum leprosum. Lamprene has not been demonstrated to be effective in the treatment of other leprosy associated inflammatory reactions.

Combination drug therapy has been recommended for initial treatment of multibacillary leprosy to prevent the development of drug resistance.

### CONTRAINDICATIONS

There are no known contraindications.

### WARNINGS

**Severe abdominal symptoms (see below) have necessitated exploratory laparotomies in some patients receiving Lamprene. Rare reports have included splenic infarction, bowel obstruction, and gastrointestinal bleeding. There have also been reports of death following severe abdominal symptoms. Autopsies have revealed crystalline deposits of clofazimine in various tissues including the intestinal mucosa, liver, spleen, and mesenteric lymph nodes.**

Lamprene should be used with caution in patients who have gastrointestinal problems such as abdominal pain and diarrhea. Dosages of Lamprene of more than 100 mg daily should be given for as short a period as possible and only under close medical supervision. If a patient complains of colicky or burning pain in the abdomen, nausea, vomiting, or diarrhea, the dose should be reduced, and if necessary, the interval between doses should be increased, or the drug should be discontinued.

### PRECAUTIONS

#### General

Physicians should be aware that skin discoloration due to Lamprene may result in depression. Two suicides have been reported in patients receiving Lamprene.

For skin dryness and ichthyosis, oil can be applied to the skin.

#### Information for Patients

Patients should be warned that Lamprene may cause a discoloration of the skin from red to brownish black, as well as discoloration of the conjunctivae, lacrimal fluid, sweat, sputum, urine, and feces. Patients should be advised that skin discoloration, although reversible, may take several months or years to disappear after the conclusion of therapy with Lamprene.

Patients should be told to take Lamprene with meals.

#### Drug Interactions

Preliminary data which suggest that dapsone may inhibit the anti-inflammatory activity of Lamprene have not been confirmed. If leprosy-associated inflammatory reactions develop in patients being treated with dapsone and clofazimine, it is still advisable to continue treatment with both drugs.

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in animals have not been conducted with Lamprene. Results of mutagenicity studies (Ames test) were negative. There was some evidence of impaired fertility in one study in rats treated at a dose 25 times the usual human dose: the number of offspring was reduced and there was a lower proportion of implantations.

#### Pregnancy Category C

Lamprene was not teratogenic in laboratory animals at dose levels equivalent to 8 times (rabbit) and 25 times (rat) the usual human daily dose. However, there was evidence of fetotoxicity in the mouse at 12-25 times the human dose (i.e., retardation of fetal skull ossification, increased incidence of abortions and stillbirths, and impaired neonatal survival). The skin and fatty tissue of offspring became discolored approximately 3 days after birth, which was attributed to the presence of Lamprene in the maternal milk.

It has been found that Lamprene crosses the human placenta. The skin of infants born to women who had received the drug during pregnancy was found to be deeply pigmented at birth. No evidence of teratogenicity was found in these infants. There are no adequate and well-controlled studies in pregnant women. Lamprene should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

#### Nursing Mothers

Lamprene is excreted in the milk of nursing mothers. Lamprene should not be administered to a nursing woman unless clearly indicated.

#### Pediatric Use

Safety and effectiveness in children have not been established. Several cases of children treated with Lamprene have been reported in the literature.

### ADVERSE REACTIONS

In general, Lamprene is well tolerated when administered in dosages no greater than 100 mg daily. The most consistent adverse reactions are usually dose related and are usually reversible when Lamprene is discontinued.

#### Adverse Reactions Occurring in More Than 1% of Patients

*Skin*: Pigmentation (from pink to brownish-black) in 75-100% of the patients within a few weeks of treatment; ichthyosis and dryness (6-28%); rash and pruritus (1.5%).

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

*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 ESR.

#### Adverse Reactions Occurring in Less Than 1% of Patients

*Skin*: Phototoxicity, erythroderma, acneiform eruptions.

monilial cheilosis

*Gastrointestinal:* Bowel obstruction (see WARNINGS), gastrointestinal bleeding (see WARNINGS), anorexia, constipation, weight loss, hepatitis, jaundice, eosinophilic enteritis, enlarged liver

*Ocular:* Diminished vision

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

*Psychiatric:* Depression secondary to skin discoloration; two suicides have been reported.

*Laboratory:* Elevated levels of albumin, serum bilirubin, and AST (SGOT); eosinophilia; hypokalemia

*Other:* Splenic infarction (see WARNINGS), thromboembolism, anemia, cystitis, bone pain, edema, fever, lymphadenopathy, vascular pain

## 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.

## DOSAGE AND ADMINISTRATION

Lamprene should be taken with meals

Lamprene should be used preferably in combination with one or more other antileprosy agents to prevent the emergence of drug resistance

For the treatment of proven dapsone-resistant leprosy, Lamprene should be given at a dosage of 100 mg daily in combination with one or more other antileprosy drugs for 3 years, followed by monotherapy with 100 mg of Lamprene daily. Clinical improvement usually can be detected between the first and third months of treatment and is usually clearly evident by the sixth month.

For dapsone-sensitive multibacillary leprosy, a combination therapy with two other antileprosy drugs is recommended. The triple-drug regimen should be given for at least 2 years and continued, if possible, until negative skin smears are obtained. At this time, monotherapy with an appropriate antileprosy drug can be instituted.

The treatment of erythema nodosum leprosum reactions depends on the severity of symptoms. In general, the basic antileprosy treatment should be continued, and if nerve injury or skin ulceration is threatened, corticosteroids should be given. Where prolonged corticosteroid therapy becomes necessary, Lamprene administered at dosages of 100 mg to 200 mg daily for up to 3 months may be useful in eliminating or reducing corticosteroid requirements. Dosages above 200 mg daily are not recommended, and the dosage should be tapered to 100 mg daily as quickly as possible after the reactive episode is controlled. The patient must remain under medical surveillance.

For advice about combination drug regimens, contact the USPHS Gillis W. Long Hansen's Disease Center, Carville, LA (504-642-7771)

## HOW SUPPLIED

*Capsules* 50 mg—brown, spherical
Bottles of 100 ..... NDC 0028-0108-01

Capsules 100 mg—brown, oblong (imprinted GEIGY GM)
Bottles of 100 ..... NDC 0028-0109-01

Do not store above 86°F. Protect from moisture.

*Dispense in tight container (USP).*

667750 Printed in U.S.A. C86-66 (Rev. 12/86)

Dist. by:
GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

**Geigy**

MED

REV

July 10, 1986

Medical Officer's Review #4 of NDA 19-500

Sponsor: Ciba-Geigy

Name of Drug: Clofazimine

The submission dated 6/27/86 consists of revised draft labelling with references. Also included is a revision of Table 15A.

Table 15A shows antibacterial efficacy in ENL patients treated with Lamprene alone:

| | Original Table Lamprene + Concomitant Therapy | | Revised Table Lamprene alone | |
|---|---|---|---|---|
| | No. | Value | No. | Value |
| BI drop to 0, ENL Median duration treatment | 15 | 6.9 y | 15A | 7.8 y |

All ENL case report forms in Vol. 29 were examined to verify the Revised Table 15A.

Case 2953 is recorded correctly in the Table 15A. However, clofazimine use at 200 mg/day apparently led to a laparotomy which was not reported in the Adverse Experience tables.

Case 2963 is recorded correctly in Table 15A. The patient experienced 10 pound weight loss, abnormal GI series and discontinued drug and NHDC treatment himself.

Case 2974 is correctly reported in Table 15A. She was not evaluated for reduction or elimination of corticosteroid therapy. The patient discontinued treatment due to pigmentation.

Case 2979 is correctly reported in Table 15A.

Conclusions: The claim for efficacy in ENL stands even after eliminating patients receiving concomitant therapy.

Recommendation: The sponsor should carefully summarize all adverse events, and be certain that all drug-related laparotomies are included. (See also previous MOR's re: summarizing adverse events).

Draft Labelling dated 6/27/86 and edited by Dr. Tabor:
The following still need to be addressed:

1. Pharmacokinetics. The source of the data used to write the pharmacokinetics section needs to be identified. The term "fecal elimination" is more appropriate than "fecal excretion."

2. Reference 1 should be indicated at the appropriate place in the labelling.

3. Indications and Usage. If the 200 mg dose for ENL is to be included, the 100 mg dose for lepromatous leprosy should also be included.

4. Warnings. A box warning is appropriate, since according to the CFR, the FDA may require one for "special problems, particularly those that may lead to death or serious injury." This would apply to the GI deaths, laparotomies, and thromboembolic episodes and deaths. The numbers of deaths and laparotomies should be given. It should be clarified that tissue deposits of clofazimine have been found even after accidental death.

5. Precautions. The advice regarding treatment of skin with oil should be left in this section as well as the next as "Patient Information" may not be read by MDs.

6. Unless there is data to substantiate the claim that "patients should be told to take Lamprene with meals," the statement should be that "Lamprene is given with meals."

7. Drug Interactions. The first sentence should be omitted unless supporting data are provided.

8. Pregnancy Category. I agree with Mr. Davitt's memo of 7/7/86. It is not pertinent to say that skin discoloration in animals appeared after birth due to nursing, when human infants were discolored at birth. The last sentence is not appropriate; the version used in the previous draft is in accord with the CFR.

9. Adverse Reactions. Diminished vision is an unlikely adverse reaction. How do you distinguish from underlying Hansen's disease of the eye or age related changes? Suggest omitting this. Thromboembolic episodes other than spleen infarct should be included.

10. Dosage. See 6 above. Suggest revising sentence about "combination" to read "Concurrent antileprosy therapy may prevent emergence of drug resistance." Paragraph 4 implies that no therapy is required after negative skin smears are obtained. However, many experts believe that life-long therapy is necessary for lepromatous leprosy.

Recommendations: In view of the many revisions in the draft labelling, the sponsor should ask Dr. Jacobsen (NHDC) to review the proposed final draft.

SBA dated 7/7/86

IV. The teratogenicity studies should be revised per Mr. Davitt's memo of 7/7/86.

V. The two pivotal studies are not "uncontrolled." They are retrospective and historically controlled. The statement about thalidomide should be revised to say that it "may" no longer be available in the U.S. Not all deaths were included (see MORs). Unnecessary deaths due to excessive dosing and failure to recognize adverse events and reduce or stop drug would not be acceptable.

"Approvable" letter:
The letter is incomplete. See above and MOR #3. A box warning should be required. See above. The labelling points noted above should be addressed. "Psychiatric" adverse reactions. The suicides and depression may have been due to the underlying disease, not the skin discoloration.

Victoria Schauf M.D.
Victoria Schauf, M.D.

cc:
Orig NDA
HFN-340
HFN-815 ET 7/23/86
HFN-815/CSO
HFN-815/VSchauf; llm/7/22/86
1209m

7/23/86
I concur with all points in this review except submitting labeling to Dr. Jacobson. E-Tabor, M.D.

DRD 23 Jul 86

June 20, 1986

Medical Officer's #3 Review of NDA 19-500

Sponsor: Ciba-Geigy

Drug: Clofazimine
LamproneR
3-(p-chloroanilino)-10-(p-chlorophenyl-2, 10-dihydro-2-isopropyliminophenazine

The submission dated 6/19/86 contains responses to my labelling review. I have the following recommendations:

Response to Comment 1. The revised statement should read:
Lamprene inhibits mycobacterial growth and binds preferentially to mycobacterial DNA.

Response to Comment 2. The reference in Lepr. Rev does not contain data to support the claim of 70% absorption in man. If data cannot be provided to support the 70% claim, the sentence should be revised.

Response to Comment 3a. The reference (2) in the draft labelling does not contain the necessary data. Data should be provided or located in the NDA to support the claim.

Response to Comment 3b. The revised statement should adhere to the wording provided. Preceding the in vitro data, the statement should be: "The following in vitro data are available, but their clinical significance is unknown."

Response to Comment 3c. Satisfactory.

Response to Comment 3d. The in vitro data for M. tuberculosis should be left out, as otherwise it would be necessary to explain that the in vivo data for this drug do not show activity and that numerous drugs of proven value are available for M. tuberculosis. The supporting data referred to in NDA 1.1 p 53-56 for the other species do not show how many isolates of each species were tested. However, as judged from p 53-56 and the reference by Vischer, the following numbers of isolates were evaluated:

| | |
|---|---|
| M. tuberculosis | 88 |
| M. bovis | 22 |
| M. kansasii | 1 |
| M. avium | 5 |
| S. epidermidis | 2 |
| B. anthracis | 1 or 2 |
| diphtheroids | 2 |

Claims based on 1 or 2 tests are not appropriate and should be omitted.

Response to Comment 4a. The Clinical Studies section was omitted as requested. Some of the information appears now in Indications (see below).

Response to Comments 4b and c. Satisfactory.

Response to Comment 5. Satisfactory, except that the following should be added after superscript 2-4. "Combined therapy with Lamprene, rifampin, and dapsone may prevent the emergence of dapsone resistance."

Indications: The sponsor should consider rewording the Indications para 4 as follows:

> Lamprene, given at dosages of approximately 200 mg daily, is effective in lepromatous leprosy complicated by erythema nodosum leprosum. The use of Lamprene in other leprosy-associated inflammatory reactions remains controversial.

Response to Comment 6. Several points have not been satisfactorily addressed. These reflect some of the most important labelling concerns. They relate to deaths, serious disability, laparotomy, spleen and GI infarcts and how to avoid or detect these. A box warning would be appropriate. Has more than one patient experienced spleen infarct? The material from "Precautions-General" should also appear here.

Response to Comment 7. Satisfactory, except that treatment for ichthyosis should appear in Precautions-General and Patient Information, not in Adverse Effects.

Response to Comment 8. The data to support this should be provided or located in the NDA or the statements revised.

Response to Comment 9. Satisfactory.

Response to Comment 10. Pregnancy Category C is acceptable. However, it is helpful to state the reason - - impaired fertility in animals.

Response to Comment 11. The sponsor states that GI bleeding and bowel obstruction have been added to the PI, but I do not find it. Spleen infarction should also be mentioned in adverse effects.

Response to Comment 12. Satisfactory.

Response to Comment 13. Reference to Response 8 is not satisfactory (see above). No data have been submitted to support alternate day dosing. This should be provided or the recommendation rewritten. What is the NHDC recommendation for multibacillary leprosy? It is hard to recommend 50 mg daily when pivotal studies use 100-200 mg daily. It should be mentioned that some authorities believe treatment should continue indefinitely. Please explain the 300 mg daily dose recommendation for ENL. In the ENL study, initial treatment was 200 mg daily. Is single or divided dosing recommended? How long should clofazimine be continued at 100 mg daily for ENL? Would it be better to recommend dosing of 100 mg/day for lepromatous leprosy (with or without dapsone resistance) with increase to 300 mg/day for ENL?

Response to Comment 14. One AIDS reference should be retained. References need to be located as superscripts at appropriate points in the text.

Note: The above recommendations were discussed and some were amended at the 6/23/86 meeting with the sponsor.

The submission dated 6/23/86 contained revised NHDC NDA Tables 4-33 and a report of deaths possibly related to clofazimine. The new Tables 4A-33A are claimed to analyse only those patients not receiving concurrent antileprosy treatment. The tables differed as follows:

| Parameter | Original Table # | Value | Revised Table # | Value |
|---|---|---|---|---|
| Initial Lamprene Dose, Dapsone resistant leprosy Mean mg/d | 6 | 171.5 | 6A | 101.6 |
| Dose after 3 years Dapsone resistant leprosy Mean mg/d | 6 | 66.1 | 6A | 98.8 |
| Initial Lamprene Dose, ENL Mean mg/d | 13 | 181.3 | 13A | 100 |
| Dose after 3 yrs, ENL Mean mg/d | 13 | 81.2 | 13A | 100 |
| BI drop to 0, ENL Mean duration treatment | 15 | 6.9 | 15A | 11.6 |

The individual case report forms were examined to verify the content of Table 15A. The first three cases examined (2833, 2855, 2861) had all received concommitant Dapsone. I requested Ms. Ruddin to correct the Tables to remove all subjects with concimitnat anti-leprosy therapy.

Conclusion: The revised Tables still contains patients receiving concommitant therapy.

The sponsor reports 11 deaths where the investigator attributed a possible role for Lamprene in the death. One report came from NHDC and ten from the literature review as follows:

| | |
|---|---|
| Suicide | 2 |
| GI | |
| Abdominal pain, vomiting, diarrhea, and/or hypokalemia | 7 |
| Abdominal pain, diarrhea, hypoproteinemia, edema | 1 |
| Abdominal pain, and mala-absorption with extensive GI drug deposits | 1 |

This summary fails to cite several deaths known to FDA and reported to the sponsor as noted in MOR # 1. These include

| | |
|---|---|
| GI | |
| bowel infarct | 1 |
| mesenteric thrombosis | 1 |
| Deep femoral occlusion | 1 |

Recommendation:

All known Lamprene related deaths should be included in a warning in the labelling. If possible, it should be indicated whether or not the GI deaths appear to occur with high daily or total doses. A box warning concerning GI and thromboembolic deaths is appropriate since it would be used to point out a special, potentially avoidable problem which may lead to death.

Victoria Schauf, M.D.

Victoria Schauf, M.D.

cc:
Orig NDA
HFN-815 ET 7/11/86
HFN-815/CSO
HFN-340
HFN-815/VSchauf:js/6/27/86
1201m

DRS 24 Jun 86

NDA 19-500

Addendum NDA 19-500

May 14, 1986

The submission dated 5-2-86 addresses Recommendations 1-3 in the MOR. A satisfactory clinical response to therapy for dapsone resistant leprosy was defined as a favorable response in one or more of the following: no occurrence of new skin lesion, no further progression of sensory loss, no further deterioration of ophthalmologic symptoms, relief of nasopharyngeal symptoms. Diagnostic criteria for ENL for patients with active lepromatous leprosy included one or more of the following: subcutaneous erythematous painful nodule(s), fever, neuritis, arthralgia, lymphadenitis, edema, iritis, orchitis, nephritis, hepatosplenomegaly. A satsifacotory clinical response in ENL required one or more of the following: suppression of inflammatory reaction; no evidence of new crops of nodul ; disappearance of fever; improvement in neuritis, edema, iritis, orchitis, arthralgia, lymphadenitis.

Also included is the requested safety summary which was published by Ciba-Geigy personnel in the Proceedings of the XII International Leprosy Congress, New Delhi, India, Feb 20-25, 1984. Results of a questionnaire were reported for 31 institutions treating 2034 patients with and 4261 patients without ENL. Dosage ranged from 200 mg/wk to 300 mg/d over a period of 15 months to 10 years. Side effects included: skin discoloration, 48-93%, depending on dose; dry skin, 10-29%; pruritus, 0-1%; pigmentation of conjunctiva or sclera, 1-6%, depending on dose; pigmentation of cornea (rare); impaired vision of unknown ethiology 1-2%; nausea, abdominal pain, and/or [illegible], [illegible]%, depending on dose; melena, weight loss, constipation, [illegible] hydria, regional enteritis (rare); withdrawal of [illegible] 0.5-1.4%, depending on dose. There were 22 [illegible] One hospital reported three sudden, unexplained [illegible] deaths were attributable to clofazimine.

[illegible] sponsor still should address the following: Recommendation [illegible] Jacobson's comment on GI obstruction; summary of all [illegible] deaths; labelling changes.

Victoria Schauf MD.

Victoria Schauf, M.D.

5/22/86 Division Director's Comment

On p. 3 of M.O.R., 100% have "satisfactory respo[illegible] defined here as including "no further progression". What is known about incidence of "no further prog[illegible] prior to use of clofazimine in dapsone-resistant patients? M.O.R. p. 3 says "spontaneous remiss[illegible] was "essentially zero".

If 4/5 randomly selected case reports show prior or concurrent use of other drugs, does this affect conclusions? Should indications state this more definitively. In the ENL study, if "no evidence of new ... as a criterion for clinical response, what is the likelihood of this occurring spontaneously?

cc:
Orig NDA
HFN-340
HFN-815 ET 5/22/86
HFN-815/CSO
HFN-815/VSchauf/11m/5/15/86
1062m

[illegible] 16 May 86

Addendum to Medical Officer's Review #1 of NDA 19-500

April 11, 1986

Drug: Clofazimine

Sponsor: Ciba-Geigy

Recommendations for Labeling:

After meeting with Mr. Carlin and Mr. Davitt, I have the following additional recommendations:

1. The sponsor should indicate to FDA whether or not the dosage form used to determine absorption, serum concentrations, and any other human pharmacologic data as cited in the labeling is the same dosage form as the NDA product. If not, address this and revise the labeling appropriately.

2. Page 2, 3 lines from the bottom of draft labeling, delete "However."

3. Provide an explanation to Mr. Carlin of the high mortality in 6 month rat study at drug doses similar to those proposed in man and in the placebo group.

4. Report any lung changes at autopsy in humans treated with the drug

(drug-related and incidental deaths).

5. Delete statement on Ames test and state: "Adequate mutagenicity studies have not been done."

6. No $LD_{50}$ data ~~is~~ necessary in the labeling.

7. Mr. Carlin and Mr. Davitt are to provide me further input regarding fertility and pregnancy statements in labeling.

Victoria Schauf MD
Victoria Schauf, M.D.

cc:

Orig NDA

HFN-340

HFN-815 E. T. 4/17/86

HFN-815/CSO

HFN-815/VSchauf/llm/4/14/86

0957m

4/17/86
Division Director's Comments:
The NDA is still under review for efficacy. However, the comments in this labeling review may be transmitted.
E. Tabor, M.D

June 5, 1986

Medical Officer's Review #2 of NDA 19-500

Sponsor: Ciba-Geigy
Summit, New Jersey 07901

Name of Drug: clofazimine
Lamprene[R]

This submission dated 5/21/86 includes tables of concomitant medications for the Hansen's Center patients. In the dapsone resistant group, 56 of 80 patients received no concomitant therapy, according to the sponsor. In the ENL group, 24 of 49 patients are said to have received no concomitant anti-leprosy therapy; however, the number receiving concomitant anti-inflammatory therapy is not shown. In the latter study, it is said that 36 of 49 patients had been treated with steroids and/or ACTH prior to therapy and that with treatment, steroid requirements were reduced in 32 (89%) patients. As previously noted, Dr. Jacobson of NHDC was quoted saying "the use of steroids could be eliminated two to six months after the start of clofazimine therapy in a majority of ENL patients."

Recommendations: Although the NDA is approvable, several items need to be addressed. These include:

1. Reconstruct NHDC NDA Table 4-33 using only data from patients not receiving concurrent anti-leprosy therapy.

2. Labelling revisions per previous reviews.

3. Clarification of Dr. Jacobson's comment on GI distruction.

4. Report and summarize all clofazimine related deaths of which the sponsor is aware, including those reported under other INDs.

5. What is known about the incidence of "no further progression prior to use of clofazimine in dapsone resistant patients?"

6. What is the incidence of the spontaneous occurrence of "no evidence of new nodules" in ENL?

Victoria Schauf, MD
Victoria Schauf, M.D.

cc:
Orig NDA
HFN-815 T 6/11/86
HFN-815/CSO
HFN-340
R/D initialed by ETabor:6/6/86
HFN-815/VSchauf:js/6/9/86
1121m

MKD 9Jun86

NDA 19,500

November 28, 1986

Medical Officer's Review

Sponsor: Ciba-Geigy Corporation
Summit, New Jersey 07901

Drug: Clofazimine (Lamprene(R))

Topic: "Labeling of the Pharmacokinetic Section"

The sponsor has submitted several published articles in support of the pharmacokinetic subsection in the labeling of the drug clofazimine.

The labeling information on Lamprene(R)'s absorption states that "Lamprene(R) has a variable absorption rate in Leprosy patients, ranging from 45-62% after oral administration."
To support the above statement, Mathur A, et al (Indian Journal Lepr. (India) Jan-Mar 1985, 57(1) pages 146-8) studied the absorption of the drug in lepromatous leprosy patients. Single doses of 600 mg, 400 mg, 300 mg and 100 mg were given to patients, and the amount of clofazimine present in total fecal excretion was determined. The percentage of absorption after 100 mg was 62.5%. The percentages of absorption after 600 mg, 400 mg and 300mg was 45%.

Comments:

The statement as written in the labeling about absorption rate is correct.

Serum levels
The labeling states that the "average serum concentrations in leprosy patients treated with 100 mg and 300 mg daily were 0.7 ug/ml and 1.0 ug/ml respectively."
The pharmacokinetics studies done in man by Banerjee et al (Ref: American Journal of Tropical Medicine and Hygiene 23(6); 1110-1115, November 74) supports that statement. Clofazimine 100 mg twice weekly up to 400 mg daily were given to man for a period of up to 4 years. Serum samples were obtained 1-3 hours (mean 2 hours) after 100 mg dose first thing in the morning. Another dose of 100 mg was given and further samples obtained 2 hours later. The results showed that with 100 mg twice weekly, serum levels were 0.5 ug/ml; 100 mg daily - 0.7 ug/ml, 300 mg daily - 1.0 ug/ml. 400 mg daily - 1.4 ug/ml.

Comment

The statement as written in the labeling is correct.

Elimination

"After ingestion of a single dose of 300 mg, elimination of unchanged Lamprene and its metabolites in a 24 hour urine collection was negligible."

To support that statement, Banerjee et al in their published article state that when clofazimine was given to healthy volunteers at a daily dose of 300 mg, <1 mg of drug was found in the urine. Paul Feng et al at the Johns Hopkins School of Medicine studied the metabolism also, and found that the percentage of excretion of clofazimine in 24 hour urine collection of 3

different metabolites was 0.19%, 0.28% and 0.25% after 300 mg daily oral dose.

Comments:

The statement on elimination of drug in the labeling is correct.

Half-Life

The labeling states "The half-life of Lamprene following repeated doses is estimated to be at least 70 days."
Two articles given as references support this statement.
The study done by Banerjee et al and published in November 1974 in the American Journal of Tropical medicine, and one done by Louis Levy and also published in the same journal in November 1974; 23(6) pages 1097-1109. Both studies show that the half-life of clofazimine is approximately 70 days.

Comment:

The statement on the half-life of clofazimine is correct.

Accumulation of Clofazimine in Tissues

The article by Richard E. Mansfield on Tissue Concentrations of Clofazimine in Man (Ref: American Journal of Tropical Medicine and Hygiene, 23(6) pages 1116-1119, November 1974) points out that 4 patients in whom, the tissue distribution of clofazimine was studied, 3 of the reports are autopsy reports and one is a skin biopsy report. In the first autopsy report, the highest concentration of the drug was found in the liver, lung, kidneys and body fat.
2nd autopsy report, liver, lymphnodes, adrenals, nerves, body fat and gall bladder were the tissues of maximum concentrations of the drug.
3rd autopsy report, clofazimine was found in the spleen, lung, lymphnodes and fat.
The 4th report was from a skin biopsy and showed that the body fat concentrates drug more than the skin.
In all patients, the brain concentration was near zero.
Varying amounts of drug was found in muscles and nerves. Of particular interest was that though the drug was present in the nerves, the nerves weren't discolorized. Overall, there was a high concentration of drug in the gall bladder and bile which suggests the importance of biliary route of elimination of drug.

Comment:

The last paragraph under Pharmacokinetics in the labeling addresses the tissue concentrations of clofazimine, and the statements written in the labeling are revisions.

In summary, the Pharmacokinetic subsection in the labeling correctly reflects the absorption rate, half-life, serum levels, elimination and accumulation of the drug clofazimine and does not require any revisions.

Nasim Moledina

Nasim Moledina, M.D.

cc:
Orig NDA
HFN-340
HFN-815 ET 12/3/86
HFN-815/CSO
HFN-815/NMoledina:bam:11/28/86:1811m

SRO 1 Dec 86

CHEM

REV

Division of Anti-Infective Drugs

NDA 19-500 August 7, 1985

Geigy Pharmaceuticals
Div. of Ciba-Geigy Corp.
556 Morris Avenue
Summit, New Jersey 07901

Proprietary Name: Lamprene (clofazimine) Capsules.

Dosage Form & Route of Administration:

Product is a soft gelatin capsule containing either 50 or 100 mg of active ingredient for oral use.

Pharmaceutical Category / Principal Indication:

Drug is an antibacterial and is used primarily in the treatment of Hansen's disease (Leprosy).

Structural Formula & Chemical Name:

See page 2.

Related NDA's etc.

Remarks: Sponsor requests use of a 5 year expiry for this product, we are in agreement that with the labeling storage statements that this should be allowed.

Conclusions: Controls are adequate for approval.
Labeling (in draft) is adequate fro m a controls standpoint.
We choose to waive the validation of the methodology since there is nothing novel in the methods.
Plants are in compliance at this time.

cc:
Original NDA
HFN-815 File Copy
HFN-815 CSO /Linkous
HFN-815 M.O.
HFN-815 Dr. Casola
8/7/85RCBieneman

R. C. Bieneman Chemist HFN-815

ARC 8/7/85

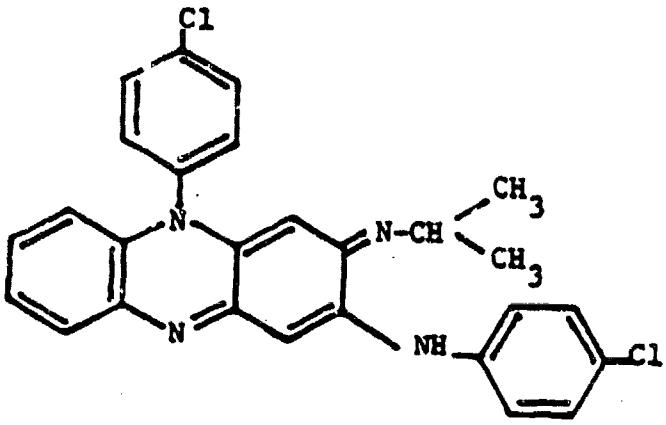
# NOMENCLATURE AND CHEMISTRY

## I. Nomenclature

| | | |
|---|---|---|
| A. | Proprietary Name: | Lamprene |
| B. | Non-proprietary Name: | Clofazimine |
| C. | Chemical Name: | 3-(p-Chloroanilino)-10-(p-chlorophenyl)-2,10-dihydro-2-isopropyliminophenazine |
| D. | Research Number: | G 30320 |
| E. | Chemical Abstracts Number: | CAS-2030-63-9 |

## II. Chemistry

A. Structure:




| | | |
|---|---|---|
| B. | Molecular Formula: | $C_{27}H_{22}Cl_2N_4$ |
| C. | Molecular Weight: | 473.4 |
| D. | Description: | A reddish-brown powder |
| E. | Solubility: | Readily soluble in benzene; soluble in chloroform; poorly soluble in acetone and in ethyl acetate; sparingly soluble in methanol and in ethanol; virtually insoluble in water. |

D. M. Kender 10/16/84

D. N. Kender, Ph.D. Date
Manager

NDA 19-500

CFR 21 -- 314.1(c)

4. Labeling: Labeling is adequate ( in draft) for a prescription drug product.

5. Drug will be restricted to Rx distribution.

6 & 7 Components & Composition:
See following 2 pages .

8a & 8 b Facilities & Personnel:

We are referenced to the following
Ciba-Geigy in Basle, Switzerland
Ciba-Geigy in Suffern, N.Y.
Ciba-Geigy in Summit, N.J.

8c Synthesis:

*8d Raw Materials:

NDA 19-500

CFR 21 -- 314.1(c) continued

8e Lot Numbers: Satisfactory see Master Files cited in 8a.

8f Other Firms:

New drug substance is manufactured by Ciba-Geigy in Basle, Switzerland
Dosage form of the drug is manufactured by and the product is packaged at either the Ciba-Geigy plant at Suffern, N.Y or Summit, N.J.

8g Batch Records:
Satisfactory see cited in 8a.

8h Instructions etc.:
A short description of the encapsulation and manufacturing process is given.
See

8i Containers:

Package is an amber glass bottle with a lined metal cap.
The bulk package shipped from switzerland to the Ciba-Geigy packaging facilities is sealed polyethylene bags in fiber drums which have sealed lids.

8j Check Weights:

Satisfactory , see cited in 8a.

8k Yield Precaution:

Satisfactory, see cited in 8a.

8l Yield:

Satisfactory, see cited in 8a.

8m Packaging & Labeling:

Satisfactory, see

8n Controls:

For the product as received in the U.S. the firm will run a U.V. assay and a thin layer assay which is stability indicating and a U.V. identity method. Other parameters will be accepted on the basis of the suppliers analysis.

The Methods used for release in Switzerland are the same and also include Average capsule weight and

NDA 19-500

CFR 21 -- 314.1(c) continued

8n continued.

standard deviation. A disintegration is also run.

Analysis of two commercial batches are submitted.

Sponsor presents a Method Validation which gives the accuracy and precision of the method and shows the linearity also.

Data on the reference standard is given in this section also.

8o Control Numbers :
Satisfactory, see 8a.

8p Stability:

Sponsor will use the following storage legend.
" Do not store above 86°F."
" Protect from Moisture".

Sponsor will also use the "Dispense in tight container (USP)''.

Sponsor proposes to incorporate batches into an ongoing stability program and withdraw any batches out of specification etc.

Data presented ,

We believe that the sponsors requested 5 year expiry is justified taking into account the data presented and the fact that the product has been a commercial item for a number of years.

8q Additional Procedures:

Satisfactory, see 8a.

NDA 19-500

CFR 21 -- 314.1(c) continued

9. Samples: Samples are available on request.
We do not propose to validate the analytical procedures used for this drug product since there is nothing novel or differant about them
The firm has presented a validation which shows the accuracy, precision and linearity of the methods when used on

Inspection, attached is the memo from HFN-325 showing that at present the firms involved are operating within our good manufacturing practice regulations.

DEPARTMENT OF HEALTH & HUMAN SERVICES

5 F 7/19

# Memorandum

TO :Manufacturing Review Branch (HFN-322) 325 DATE: July 15, 1985
Division of Drug Quality Compliance

FROM :Division of Anti-Infective Drugs HFN-815
Requester's Name R. C. Bioneman PHONE: 4436714

SUBJECT: ESTABLISHMENT EVALUATION REQUEST

NDA, ANDA, AND SUPPLEMENT NUMBER: 19-500 ( new application)

DRUG TRADE MARK (if any) Lamprene (clofazimine) Capsules

DRUG NONPROPRIETARY NAME: clofazimine

DOSAGE FORM AND STRENGTH(S): 50 & 100 mg soft gelatin capsules

DRUG CLASSIFICATION: (Priority) 1-B ~~A or B~~ 1C Other PROFILE CLASS CODE: CSG

APPLICANT'S NAME: Geigy Pharmaceuticals Division of Ciba-Geigy Corp.
ADDRESS: Summit, New Jersey 07901

FACILITIES TO BE EVALUATED: (Name, Full Address, DMF# (if any), and Responsibility)

CIBA-GEIGY ET 9/12 IC
Basle, Switzerland

ET IC

CIGS ET 7/87 CIGS ET 10/87 IC
Ciba-Geigy Ciba-Geigy
Suffern, N.Y. Summit, New Jersey

Comments: ( ) See Attached.
( ) Actual on-site inspection requested.

Reason: This drug has been given "Orphan" status.

**********

FOR HFN-322 USE ONLY:

Request Rec'd: Inspection Requested: (if applicable)

Firm(s) are in Compliance With GMPs: approvable
Basis for Decision:
Reviewing CSO: 7/19/85 Concurrance:

cc: HFN-
HFN-
HFN-322

Chemist's Review of Supplement Providing
For Voluntary Declaration of Inactive Ingredients
in Labeling Under 21 CFR 314.70(c)(2)

NDA 19-500/S-002 Dated : March 09, 1989.

Proprietary Name: Lamprene Capsules

Established Name: Clofazimine (USAN)

Dosage Form:Oral,HG Capsules Strength(s): 50 mg and 100 mg.

Applicant's Name and Address:
Ciba-Geigy Corporation
Summit , New Jersey 07901

| | YES | NO |
|---|---|---|
| Are inactive ingredients declared in the Description section of the product package insert ? | _X_ | ___ |
| Are all inactive ingredients declared ? | _X_ | ___ |
| If not, is the rationale offered for the omission ? | ___ | ___ |
| Are active ingredients declared by established names ? | _X_ | ___ |
| Are all declared inactive ingredients approved in the NDA ? | _X_ | ___ |

Provide the date of implementation: _September 1987_____

If labeling of this product is common to another NDA, provide the NDA number(s),drug name(s), dosage form(s), and strength( ).

Comments: Labeling revision not common to other NDA. The revisions to the product package insert address chemistry control issues in the "Description" section of the PPI only and do not include revisions in other sections of the labeling.
From the standpoint of chemistry and manufacturing controls, this supplement may be approved.
Action: Approval_X_; Approvable___; Not Approvable___; Additional information requested by tel.____, letter____,meeting____.

John A. Richman , Ph.D.
Reviewing Chemist HFD-530
Date Completed:03/29/89

John W. Taylor, Ph.D.
Supervisory Chemist HFD-530
Date: 03/29/89

MAR 30 1989

# DIVISION OF ANTIVIRAL DRUG PRODUCTS HFD-530

## Review of Chemistry and Manufacturing Controls

NDA 19-500/S-002 DATED:03/09/89 CDB DATE:03/14/89 REV.#1/jr

Submission Type: Labeling controls supplement, voluntary declaration of excipients.

Reviewer: J. A. Richman

APPLICANT/SPONSOR:
Ciba-Geigy Corporation
Sunnit , New Jersey 07901

Tel. (201) 277-5000

Assigned Date: 03/28/89

Completed Date:03/29/89

Route of Adm:Oral

Dosage Form(s):Capsule

Strength(s): 50 mg and 100 mg.

DrugCategory:Antileprotic agent.

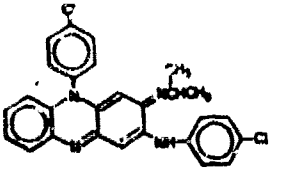
Indications:Treatment of lepromatous leprosy, including Dapsone-resistant leprosy.

PRODUCT NAME(S):
Proprietary: Lamprene Capsules

Nonproprietary: clofazimine

Code#

STRUCTURAL FORMULA - CHEMICAL NAME:



Molecular Formula:$C_{27}H_{22}Cl_2N_4$

Molecular Weight : 473.40 Dal.

3-(p-chloroanilino)-10-(p-chlorophenyl)-2,10-dihydro-2-isopropyliminophenazine.

SUMMARY / CONCLUSIONS / RECOMMENDATIONS:
This supplement is submitted in accord with PMA guidelines of 12/05/84, in agreement with FDA's Robert Temple and Elaine Esber, to provide for voluntary listing of inactive ingredients in prescription drug labeling under 21 CFR 314.70(c)(2). Refer to page 2 of this review for "Check Off" items required for approval. No revisions to the PPI text other than the "Description" section are involved in this supplement. The chemistry controls for this supplement are satisfactory and from the standpoint of chemistry and manufacturing controls , the supplement may be approved. Recommendations: Approved letter should issue.

cc:NDA 19-500 Orig.
[redacted]
HFD-530/DBirnkrant
HFD-530/MHamrell
HFD-530/JTaylor 3/30/89
HFD-530/DIsom
HFD-530/JRichman
HFD-530/POsterberg

John A. Richman , Ph.D.
Reviewing Chemist HFD-530

PHARM

REV

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics

---

Date: July 7, 1986

To: Director
Division of Anti-Infective Drug Products, HFN-815

From: Supervisory Pharmacologist
Division of Anti-Infective Drug Products, HFN-815

Subject: Clofazimine (Lamprene) NDA 19-500

Ciba-Geigy's summary of the reproduction study findings (copy appended) implies that adverse effects encountered in the mouse could well be secondary to maternal toxicity, i.e., not a reflection of direct fetotoxicity. But the submitted reports are far from clear in this regard. Unless they can provide a convincing argument to the contrary, the mouse findings (which further justify Category C) should be included in the Pregnancy statement.

I suggest the following text to replace the first sentence in the current draft:

> "Lamprene was not teratogenic in laboratory animals at dose levels equivalent to 8 times (rabbit) or 25 times (rat) the usual human daily dose. However, there was evidence of fetotoxicity in the mouse at 12-25 times the human dose; i.e., retardation of fetal skull ossification, increased incidence of abortions and stillbirths, and impaired neonatal survival."

In all other respects, the draft approvable letter is satisfactory.

John M. Davitt

cc:
Orig NDA
HFN-815
HFN-815/CSO
HFN-815/HCarlin
HFN-815/JDavitt:js/7/7/86
1248m

Rec'd 7/8/86
ET 7/8/86

## SUMMARY OF TERATOLOGY STUDIES WITH LAMPRENE

| Species | Dose Level(s) | Key Findings |
|---|---|---|
| Mouse | 0,5,25, or 50 mg/kg | 1) Fetal toxicity is strongly correlated with maternal toxicity<br>2) No evidence of a primary embryopathic effect<br>3) No evidence of teratogenic effects |
| Rat | 0,5,25, or 50 mg/kg | 1) No evidence of embryotoxic or teratogenic effects |
| Rabbit | 0,5, or 15 mg/kg | 1) No evidence of embryotoxic or teratogenic effects |