CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 74928

Trade Name Nicardipine Hydrochloride Capsule 20mg and 30mg.

Generic Name Nicardipine Hydrochloride Capsule 20mg and 30mg

Sponsor Lipha Pharmaceuticals, Inc.
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Application Number 74928

APPROVAL LETTER
Lipha Pharmaceuticals, Inc.
U.S. Agent for Genpharm, Inc.
Attention: Anita M. Goodman, M.D.
9 West 57th Street, Suite 3825
New York, NY 10019-2701

Dear Madam:

This is in reference to your abbreviated new drug application dated July 16, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Nicardipine Hydrochloride Capsules, 20 mg and 30 mg.

Reference is also made to your amendments dated October 23, 1996; January 3, March 12, June 4, June 25, September 5, and December 15 1997; and March 11, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Nicardipine Hydrochloride Capsules, 20 mg and 30 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Cardene® Capsules, 20 mg and 30 mg, respectively, of Syntex Laboratories, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.
We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74928

FINAL PRINTED LABELING
USUAL DOSAGE: One capsule three times a day.
SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

NDC 55567-042-25 500 Capsules

NICARDIPINE HYDROCHLORIDE CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by:
GENPHARM INC.
Toronto, Canada
M8Z 2S6

STORE AT ROOM TEMPERATURE BETWEEN 15°C AND 30°C (59°F AND 86°F).
DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINERS.
USUAL DOSAGE: One capsule three times a day.

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

003-173 REV.#00

NDC 55567-041-25 500 Capsules

NICARDIPINE HYDROCHLORIDE CAPSULES

20 mg

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by:
GENPHARM INC.
Toronto, Canada
M6Z 2S6

STORE AT ROOM TEMPERATURE BETWEEN 15° and 30°C (59° and 86°F).

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINERS.
NICARDIPINE HYDROCHLORIDE
CAPSULES

DESCRIPTION

Nicardipine hydrochloride capsules contain nicardipine hydrochloride, a calcium channel blocking drug. Nicardipine hydrochloride is a calcium channel blocker. 

Mechanism of Action

Nicardipine hydrochloride is a calcium channel blocker. It reduces the membrane permeability of calcium ions, which results in a decrease in the production of platelet aggregating factor. This decrease in platelet aggregating factor reduces the formation of thrombin, which prevents clot formation and reduces the risk of thrombosis.

CLINICAL PHARMACOLOGY

Absorption

Nicardipine is rapidly absorbed after oral administration. The bioavailability of nicardipine is approximately 90%. The peak plasma concentration occurs within 1 to 2 hours after oral administration.

Distribution

Nicardipine is widely distributed throughout the body. The drug distributes rapidly into the intravascular and extravascular tissues. It is highly protein-bound, with a binding capacity of 99%. The volume of distribution is approximately 60 to 70 liters per kilogram.

Metabolism

Nicardipine is metabolized primarily in the liver. The major metabolites are nicotine and nicardipine. The metabolic pathway involves demethylation and hydroxylation. The metabolites are excreted in the urine and feces.

Excretion

Nicardipine is excreted primarily in the urine. The elimination half-life of nicardipine is approximately 9 hours. Nicardipine is also excreted in the feces, with approximately 10% of the dose excreted in the feces.

CLINICAL PHARMACOKINETICS

Nicardipine is a potent calcium antagonist. It is rapidly absorbed after oral administration and has a short onset of action. The peak plasma concentration is reached within 1 to 2 hours after oral administration.

Indications

Nicardipine is indicated for the treatment of hypertension. It is used in the management of hypertension in patients with mild to moderate hypertension. Nicardipine is also used in the management of hypertension in patients with congestive heart failure.

Contraindications

Nicardipine is contraindicated in patients with a history of allergy to nicardipine or any of its components. It is also contraindicated in patients with a history of severe allergic reactions to other calcium channel blockers. Nicardipine is contraindicated in patients with a history of angina pectoris, recent myocardial infarction, or congestive heart failure.

Warnings

Nicardipine should be used with caution in patients with a history of bronchospastic disorders, including asthma and chronic obstructive pulmonary disease. It should also be used with caution in patients with a history of gastrointestinal disorders, including peptic ulcer disease and inflammatory bowel disease.

Precautions

Nicardipine should be used with caution in patients with a history of hepatic dysfunction or renal impairment. It should also be used with caution in patients with a history of concomitant medications that may affect the concentration of nicardipine.

Adverse Reactions

The most common adverse reactions associated with nicardipine are headache, dizziness, flushing, and hypotension. Other reported adverse reactions include flushing, nausea, vomiting, diarrhea, constipation, and increased blood pressure.

DOSAGE AND ADMINISTRATION

The usual starting dose of nicardipine is 10 mg twice daily. The dose may be increased to 20 mg twice daily if necessary. The dose should be adjusted based on the patient's response to therapy.

Nicardipine is not recommended for use in patients with a body weight less than 50 kg.

Drug Interactions

Nicardipine may increase the blood pressure-lowering effect of diuretics, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers. It may also increase the risk of hypotension when used with other agents that decrease blood pressure.

Overdosage

In the event of an overdose, supportive and symptomatic therapy should be provided. Hemodialysis may be considered in patients with severe intoxication.

Nicardipine is a calcium channel blocker and is effective in the treatment of hypertension. Its mechanism of action involves reducing the membrane permeability of calcium ions, which decreases the production of platelet aggregating factor. Nicardipine is rapidly absorbed after oral administration and has a short onset of action. Its bioavailability is approximately 90%, and the peak plasma concentration occurs within 1 to 2 hours after oral administration. Nicardipine is widely distributed throughout the body and is highly protein-bound. The drug is metabolized primarily in the liver, with nicotine and nicardipine as major metabolites. Nicardipine is excreted primarily in the urine and feces.

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There is a transient increase in systolic elevation, including sodium. Nifedipine does not cause generalized fluid retention, as measured by weight change, although 17% to 3% of the patient population gained weight.

Effects on Angina Pain

in controlled oral studies (at a dosage of 40 to 60 mg/day) in patients with chronic stable angina, nifedipine increased the time to appearance of angina pectoris during daily activity. The frequency of exercises at systolic blood pressures 100 to 120 mm Hg was also increased, but the nifedipine-induced decline in systolic blood pressure was not accompanied by a decrease in systolic or diastolic blood pressure. Nifedipine also increased the time to appearance of angina pectoris during the holdoff period of the holdoff studies. The decline in systolic blood pressure was demonstrated to be two hours post-dosing (though the diastolic blood pressure remained unchanged). Blood pressure in patients with angina was about 10 mm Hg at peak blood levels and was significantly different from placebo at trough blood levels.

Effects on Hypertension

Nifedipine produced dose-related decreases in both systolic and diastolic blood pressure in clinical trials. The antihypertensive efficacy of nifedipine administered twice daily was demonstrated in three placebo-controlled studies involving 517 patients with mild to moderate hypertension. The blood pressure reduction was dose-related, and the effect was present at the end of the dosing interval. The results from placebo-controlled studies of nifedipine group showed that blood pressure was reduced by 20 mm Hg at trough blood levels.

When added to beta-blocker therapy, nifedipine further lowers both systolic and diastolic blood pressure.

1. Beta Blockers

Nifedipine hydrochloride capsules are indicated for the management of patients with chronic stable angina (effort-related angina). Nifedipine hydrochloride capsules can be taken alone or in combination with other antianginal drugs. In administering nifedipine it is important to be aware of the relatively large peak to trough differences in blood pressure effect. (See DOSAGE AND ADMINISTRATION).

2. Antiarrhythmics

Nifedipine hydrochloride capsules are indicated for the treatment of hypertension. Nifedipine hydrochloride capsules may be used alone or in combination with other antiarrhythmic drugs. In administering nifedipine it is important to be aware of the relatively large peak to trough differences in blood pressure effect. (See DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Nifedipine hydrochloride capsules are contraindicated in patients with hypersensitivity to the drug.

Because part of the effect of nifedipine is secondary to reduced afterload, the drug is also contraindicated in patients with advanced arteriosclerosis. Reduction of diastolic pressure in these patients may occur rather than improve altered oxygen balance.

WARNINGS

Nifedipine may cause uterine contractions in pregnant women. About 7% of patients in short term placebo-controlled constrictions have developed increased frequency, duration or severity of angina on starting nifedipine or at the time of dosage increase, compared with 3% of patients on placebo. Concomitant therapy with beta-blockers also show a greater frequency of increased angina, 4% to 6%. The mechanism of the effect has not been established. (See ADVERSE REACTIONS).

Use in Pregnancy

Although preliminary hemodynamic studies in patients with congestive heart failure have shown that nifedipine reduced afterload without improving myocardial contractility, there is no conclusive evidence in vivo and in some patients. Caution should be exercised when using the drug in congestive heart failure patients, particularly in combination with beta-blockers.

Beta-blocker withdrawal

Nifedipine should be administered with caution to patients who have been withdrawn from beta-blocker therapy. Of the patients who underwent withdrawal, 5% showed a reduction of the dose of beta-blocker, prematurely over 1 to 3 days.

PRECAUTIONS

Drug Interactions

Beta-blockers

In controlled clinical studies, thrombolytic beta-blocker therapy has been frequently administered concurrently with nifedipine hydrochloride capsules. The combination is well tolerated.

Calcium-channel blockers

Nifedipine increases calcium-channel blockers levels. Patients receiving the two drugs concurrently should be closely monitored.

Diuretics

Some calcium channel blockers may increase the concentration of digitalis preparations in the blood. Nifedipine usually does not alter the plasma levels of digoxin.

This interaction should be evaluated after concurrent therapy with nifedipine is started.

Aluminum and Magnesium Hydroxide

Concurrent administration of an antacid containing 600 mg aluminum hydroxide and 250 mg magnesium hydroxide had no effect on nifedipine absorption.

Pancreatitis

Since nifedipine, has been reported during trials in patients with concurrent use of a beta-blocker and a calcium-channel blocker, these data suggest that interactions were not observed in these clinical studies with nifedipine, an increase volume of circulatory fluids might be required if such an interaction were to occur.

<table>
<thead>
<tr>
<th>STYLOF. BP (mm Hg)</th>
<th>DOSTOLBP. BP (mm Hg)</th>
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<tbody>
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<tr>
<td>Trough/</td>
<td>Trough/</td>
</tr>
<tr>
<td>P</td>
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</tr>
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<td>30</td>
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</tr>
<tr>
<td>40</td>
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The responses are shown as differences in peak and time-averaged values. The large changes between peak and trough effects were not accompanied by observed effects at peak response times. In a study using 20 hour intra-arterial blood pressure monitoring, the cardiovascular variation in blood pressure remained unchanged, but the systolic and diastolic blood pressures were reduced throughout the whole 24 hours.

When added to beta-blocker therapy, nifedipine further lowers both systolic and diastolic blood pressure.

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Concomitant administration of metoprolol and propranolol results in elevated plasma propranolol levels. Plasma concentrations of propranolol should therefore be monitored when concomitant administration of metoprolol and propranolol is given to patients with heart failure or with a history of congestive heart failure.

Pregnancy

Propranolol is excreted in human milk. When used in breast feeding mothers, propranolol may cause a decrease in milk production. Propranolol should be used with caution during breast feeding.

The effects of propranolol in pregnant women are not well documented. However, propranolol is classified as Category C in the United States and Category D in other countries, and should be used with caution during pregnancy.

The effects of propranolol on the fetus were not evaluated in animal studies. Therefore, propranolol should be used during pregnancy only if clearly needed.

In rare cases, propranolol has been associated with neonatal hypoglycemia. Therefore, mothers who are taking propranolol should be instructed to monitor their blood glucose levels closely and to seek medical advice if they experience symptoms of hypoglycemia in their newborns.

Pediatric Use

Propranolol is not recommended for use in children under the age of 18 due to the potential for adverse effects.

Use in the Elderly

Propranolol is not recommended for use in elderly patients due to the potential for adverse effects.

Contraindications

Propranolol is contraindicated in patients with bradycardia, second or third-degree heart block, cardiogenic shock, severe chronic obstructive pulmonary disease, severe liver or renal impairment, and severe systemic arterial hypertension.

Adverse Reactions

Adverse reactions are generally dose-related and may include:

- Bradycardia
- Hypotension
- Dizziness
- Fatigue
- Asthenia
- Anemia
- Lactic acidosis
- Respiratory depression
- Hypersensitivity reactions

Overdose

Overdose with propranolol may result in severe bradycardia, hypotension, respiratory depression, and cardiac arrest. Treatment should include supportive care, such as intravenous fluids, atropine, and vasopressors if necessary. Administration of flumazenil may be considered in cases of suspected benzodiazepine overdose.

Notes:

1. The information provided is based on the literature and may not be comprehensive.
2. The information is intended for informational purposes only and should not be used for diagnostic or therapeutic purposes.
3. For more detailed information, please consult a healthcare professional.
Adverse Experiences

Prevalence of Patients with Adverse Effects in Clinical Studies

Table of Adverse Reactions by Class and Prevalence

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<th>Placebo (n=210)</th>
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<tr>
<td>Diarrhea</td>
<td>4.2 (89)</td>
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<td>Dizziness</td>
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<tr>
<td>Rash</td>
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<td>0.1 (2)</td>
</tr>
</tbody>
</table>

DOSAGE AND ADMINISTRATION

Adults

The dose of Nizatidine hydrochloride should be adjusted according to the patient's needs. The Nizatidine hydrochloride may be taken during or after meals, or on an empty stomach.

Special Population

Pediatric Population

Nizatidine hydrochloride is not recommended for children under the age of 12.

Concomitant Use with Other Antihistamine Agents

Nizatidine hydrochloride should be taken cautiously in patients on concurrent therapy with other antihistamines.

Contraindications

Nizatidine hydrochloride is contraindicated in patients with known hypersensitivity to Nizatidine or to any component of the formulation.

Nizatidine hydrochloride is not recommended for use in patients with known hypersensitivity to Nizatidine or to any component of the formulation.

WARNINGS

Nizatidine hydrochloride is not recommended for use in patients with known hypersensitivity to Nizatidine or to any component of the formulation.

CAUTION: Federal law prohibits dispensing without prescription.
1. **CHEMISTRY REVIEW NO.** 3

2. **ANDA** 74-928

3. **NAME AND ADDRESS OF APPLICANT**
   Genpharm Inc.
   37 Advance Road
   Etobicoke, Ontario
   Canada MBZ 286

4. **LEGAL BASIS FOR SUBMISSION**
   The applicant certifies, that to the best of it knowledge, U.S. Patent No. 3,985,758 expired on February 15, 1996 and there is no market exclusivity for the drug product subject.

   Innovator: Syntex Laboratories Inc. - Cardene®

5. **SUPPLEMENT(s)**
   N/A

6. **PROPRIETARY NAME**
   N/A

7. **NONPROPRIETARY NAME**
   Nicardipine Hydrochloride
   Capsule

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**
   N/A

9. **AMENDMENTS AND OTHER DATES:**
   **Firm:**
   7/16/96 - Original
   9/27/96 - Response to comments in acknowledgment.
   9/5/97 - Response to 2nd def. facsimile (chem. & labeling). Subject of this review.
   12/15/97 - Response to fax, MV.
   3/11/98 - Response to phone memo, limit for α-form. Subject of this review.

   **FDA:**
   9/13/96 - Acknowledgment, with comments.
   2/7/97 - 1st def. letter (chem. & labeling).
   1/31/97 - Bio. review, not acceptable.
   2/20/97 - 1st Bio. def. letter.
   8/1/97 - Bio. review, acceptable.
   8/18/97 - Bio. letter, no further questions.
   3/26/97 - MV from St. Louis, questions to firm.
   12/8/97 - Phone memo, faxed questions about MV from St. Louis to firm.
   12/17/97 - MV acceptable from St. Louis.
   2/4/98 - Phone memo

10. **PHARMACOLOGICAL CATEGORY**
    Calcium Channel Blocker

11. **Rx or OTC**
    R
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
   Capsule

14. POTENCY
   20 mg & 30 mg

15. CHEMICAL NAME AND STRUCTURE

   Nicardipine Hydrochloride
   C_{26}H_{31}N_{2}O_{3}·HCl; M.W. = 515.99

   \[
   \text{Structure Image}
   \]

   2- (Benzylmethylamino)ethyl methyl 1,4-dihydro-2,6-dimethyl-4-
   (m-nitrophenyl)-3,5-pyridinedicarboxylate monohydrochloride.
   CAS [54527-84-3]

16. RECORDS AND REPORTS
   N/A

17. COMMENTS
   EER, Bio., labeling, Method validation, and DMF acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS
   Approval

19. REVIEWER:
    Norman Gregory

   DATE COMPLETED:
    3/13/98