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.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 74928

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74928

APPROVAL LETTER

ANDA 74-928

MAR 19 1998

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.

74-928

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,

8-18-88

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


Nicardipine Hydrochloride
30 mg Capsule
Genpharm Inc.
Toronto, Canada
LOT.: XXXXXX
EXP.:XX XXXX

USUAL DOSAGE: One capsule three times a day.

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

003-170 REV.#00

NDC 55567-042-25 500 Capsules

NICARDIPINE

HYDROCHLORIDE CAPSULES

[redacted]

CAUTION: Federal law prohibits dispensing without prescription.

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

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

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINERS.

3 55567-042-25 4

000077

USUAL DOSAGE: One capsule three times a day.

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

003-170 REV.#00

NDC 55567-042-25 500 Capsules

NICARDIPINE

HYDROCHLORIDE CAPSULES

[redacted]

CAUTION: Federal law prohibits dispensing without prescription.

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

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

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINERS.

3 55567-042-25 4

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
M8Z 2S6

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

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINERS.

3 55567-041-25 7

000071

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
M8Z 2S6

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

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINERS.

3 55567-041-25 7

USUAL DOSAGE: One capsule three times a day.

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

003-171 REV.#00

NDC 55567-042-18 100 Capsules

NICARDIPINE

HYDROCHLORIDE CAPSULES

[redacted]

CAUTION: Federal law prohibits dispensing without prescription.

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

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

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINERS

3 55567-042-18 6

USUAL DOSAGE: One capsule three times a day.

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

003-171 REV.#00

NDC 55567-042-18 100 Capsules

NICARDIPINE

HYDROCHLORIDE CAPSULES

[redacted]

CAUTION: Federal law prohibits dispensing without prescription.

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

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

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINERS.

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USUAL DOSAGE: One capsule three times a day.

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

003-171 REV.#00

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NICARDIPINE

HYDROCHLORIDE CAPSULES

[redacted]

CAUTION: Federal law prohibits dispensing without prescription.

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Toronto, Canada M8Z 2S6

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CAUTION: Federal law prohibits dispensing without prescription.

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Toronto, Canada M8Z 2S6

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DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINERS.

3 55567-042-18 6

USUAL DOSAGE: One capsule three times a day.

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

003-174 REV.#00

NDC 55567-041-18 100 Capsules

NICARDIPINE

HYDROCHLORIDE CAPSULES

20 mg

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by
GENPHARM INC.
Toronto, Canada M8Z 2S6

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

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINERS.

3 55567-041-18 9

USUAL DOSAGE: One capsule three times a day.

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

003-174 REV.#00

NDC 55567-041-18 100 Capsules

NICARDIPINE

HYDROCHLORIDE CAPSULES

20 mg

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by
GENPHARM INC.
Toronto, Canada M8Z 2S6

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

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINERS.

3 55567-041-18 9

USUAL DOSAGE: One capsule three times a day.

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

003-174 REV.#00

NDC 55567-041-18 100 Capsules

NICARDIPINE

HYDROCHLORIDE CAPSULES

20 mg

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by
GENPHARM INC.
Toronto, Canada M8Z 2S6

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

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINERS.

3 55567-041-18 9

USUAL DOSAGE: One capsule three times a day.

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

003-174 REV.#00

NDC 55567-041-18 100 Capsules

NICARDIPINE

HYDROCHLORIDE CAPSULES

20 mg

CAUTION: Federal law prohibits dispensing without prescription.

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GENPHARM INC.
Toronto, Canada M8Z 2S6

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

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINERS.

3 55567-041-18 9

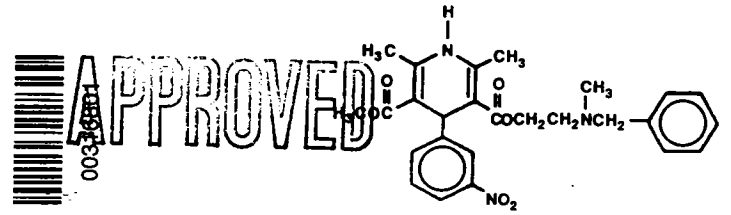
NICARDIPINE HYDROCHLORIDE

CAPSULES

DESCRIPTION

Nicardipine hydrochloride capsules for oral administration each contain 20 mg or 30 mg of nicardipine hydrochloride. Nicardipine hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium channel blocker).

Nicardipine hydrochloride is a dihydropyridine structure with the IUPAC (International Union of Pure and Applied Chemistry) chemical name 2-(benzyl-methyl amino)ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate monohydrochloride, and it has the following structural formula:



Nicardipine Hydrochloride
Molecular Formula $C_{26}H_{29}N_3O_6 \cdot HCl$

Nicardipine hydrochloride is a greenish-yellow, odorless, crystalline powder that melts at about 189°C. It is freely soluble in chloroform, methanol , and glacial acetic acid, sparingly soluble in anhydrous ethanol, slightly soluble in *n*-butanol, water, 0.01 M potassium dihydrogen phosphate, acetone, and dioxane, very slightly soluble in ethyl acetate, and practically insoluble in benzene, ether and hexane. It has a molecular weight of 515.99.

Each capsule, for oral administration, contains 20 mg or 30 mg nicardipine hydrochloride. In addition, each capsule contains the following inactive ingredients: magnesium stearate and pregelatinized starch. The capsule shell consists of FD&C Blue #1, gelatin, and titanium dioxide and is printed with black ink containing FD&C Blue #2, FD&C Red #40, FD&C Blue #1, and D&C Yellow #10.

CLINICAL PHARMACOLOGY

Mechanism of Action
Nicardipine is a calcium entry blocker (slow channel blocker or calcium ion antagonist) which inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle without changing serum calcium concentrations. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. The effects of nicardipine are more selective to vascular smooth muscle than cardiac muscle. In animal models, nicardipine produces relaxation of coronary vascular smooth muscle at drug levels which cause little or no negative inotropic effect.

Pharmacokinetics and Metabolism
Nicardipine is completely absorbed following oral doses administered as capsules. Plasma levels are detectable as early as 20 minutes following as oral dose and maximal plasma levels are observed within 30 minutes to two hours (mean T_{max} = 1 hour). While nicardipine is completely absorbed, it is subject to saturable first pass metabolism and the systemic bioavailability is about 35% following a 30 mg oral dose at steady state.

When nicardipine was administered one (1) or three (3) hours after a high fat meal, the mean Cmax and mean AUC were lower (20% to 30%) than when nicardipine was given to fasting subjects. These decreases in plasma levels observed following a meal may be significant but the clinical trials establishing the efficacy and safety of nicardipine were done in patients without regard to the timing of meals. Thus the results of these trials reflect the effects of meal-induced variability.

The pharmacokinetics of nicardipine are nonlinear due to saturable hepatic first pass metabolism. Following oral administration, increasing doses result in a disproportionate increase in plasma levels. Steady state Cmax values following 20, 30, and 40 mg doses every 8 hours averaged 36, 88, and 133 ng/mL, respectively. Hence, increasing the dose from 20 to 30 mg every 8 hours more than doubled Cmax and increasing the dose from 20 to 40 mg every 8 hours increased Cmax more than 3-fold. A similar disproportionate increase in AUC with dose was observed. Considerable inter-subject variability in plasma levels was also observed.

Post-absorption kinetics of nicardipine are also non-linear, although there is a reproducible terminal plasma half-life that averaged 8.6 hours following 30 and 40 mg doses at steady state (TID). The terminal half-life represents the elimination of less than 5% of the absorbed drug (measured by plasma concentrations). Elimination over the first 8 hours after dosing is much faster with a half-life of 2 to 4 hours. Steady state plasma levels are achieved after 2 to 3 days of TID dosing (every 8 hours) and are 2-fold higher than after a single dose.

Nicardipine is highly protein bound (>95%) in human plasma over a wide concentration range.

Nicardipine is metabolized extensively by the liver: less than 1% of intact drug is detected in the urine. Following a radioactive oral dose in solution, 60% of the radioactivity was recovered in the urine and 35% in feces. Most of the dose (over 90%) was recovered within 48 hours of dosing. Nicardipine does not induce its own metabolism and does not induce hepatic microsomal enzymes.

The steady-state pharmacokinetics of nicardipine in elderly hypertensive patients (≥65 years) are similar to those obtained in young normal adults. After one week of nicardipine hydrochloride dosing at 20 mg three times a day, the Cmax, Tmax, AUC, terminal plasma half-life, and the extent of protein binding of nicardipine observed in healthy elderly hypertensive patients did not differ significantly from those observed in young normal volunteers.

Nicardipine plasma levels were higher in patients with mild renal impairment (baseline serum creatinine concentration ranged from 1.2 to 5.5 mg/dL) than in normal subjects. After 30 mg nicardipine hydrochloride TID at steady state, Cmax and AUC were approximately 2-fold higher in these patients.

Because nicardipine is extensively metabolized by the liver, the plasma levels of the drug are influenced by changes in hepatic function. Nicardipine plasma levels were higher in patients with severe liver disease (hepatic cirrhosis confirmed by liver biopsy or presence of endoscopically-confirmed esophageal varices) than in normal subjects. After 20 mg nicardipine hydrochloride BID at steady state, Cmax and AUC were 1.8 and 4-fold higher, and the terminal half-life was prolonged to 19 hours in these patients.

Hemodynamics
In man, nicardipine produces a significant decrease in systemic vascular resistance. The degree of vasodilation and the resultant hypotensive effects are more prominent in hypertensive patients. In hypertensive patients, nicardipine reduces the blood pressure at rest and during isometric and dynamic exercise. In normotensive patients, a small decrease of about 9 mmHg in systolic and 7 mmHg in diastolic blood pressure may accompany this fall in peripheral resistance. An increase in heart rate may occur in response to the vasodilation and decrease in blood pressure, and in a few patients this heart rate increase may be pronounced. In clinical studies mean heart rate at time of peak plasma levels was usually increased by 5 to 10 beats per minute compared to placebo, with the greater increases at higher doses, while there was no difference from placebo at the end of the dosing interval. Hemodynamic studies following intravenous dosing in patients with coronary artery disease and normal or moderately abnormal left ventricular function have shown significant increases in ejection fraction and cardiac output with no significant change, or a small decrease, in the left ventricular end-diastolic pressure (LVEDP). Although there is evidence that nicardipine increases coronary blood flow, there is no evidence that this property plays any role in its effectiveness in stable angina. In patients with coronary artery disease, intracoronary administration of nicardipine caused no direct myocardial depression. Nicardipine does, however, have a negative inotropic effect in some patients with severe left ventricular dysfunction and could, in patients with very impaired function, lead to worsened failure.

"Coronary Steal", the detrimental redistribution of coronary blood flow in patients with coronary artery disease (diversion of blood from underperfused areas toward better perfused areas), has not been observed during nicardipine treatment. On the contrary, nicardipine has been shown to improve systolic shortening in normal and hypokinetic segments of myocardial muscle, and radio-nuclide angiography has confirmed that wall motion remained improved during an increase in oxygen demand. Nonetheless, occasional patients have developed increased angina upon receiving nicardipine. Whether this represents steal in those patients, or is the result of increased heart rate and decreased diastolic pressure, is not clear.

In patients with coronary artery disease nicardipine improves L.V. diastolic distensibility during the early filling phase, probably due to a faster rate of myocardial relaxation in previously underperfused areas. There is little or no effect on normal myocardium, suggesting the improvement is mainly by indirect mechanisms such as afterload reduction, and reduced ischemia. Nicardipine has no negative effect on myocardial relaxation at therapeutic doses. The clinical consequences of these properties are as yet undemonstrated.

Electrophysiologic Effects
In general, no detrimental effects on the cardiac conduction system were seen with the use of nicardipine.

Nicardipine increased the heart rate when given intravenously during acute electrophysiologic studies, and prolonged the corrected QT interval to minor degree. The sinus node recovery times and SA conduction times were not affected by the drug. The PA, AH, and HV intervals* and the functional and effective refractory periods of the atrium were not prolonged by nicardipine and the relative and effective refractory periods of the His-Purkinje system were slightly shortened after intravenous nicardipine.

*PA = conduction time from high to low right atrium, AH = conduction time from low right atrium to His bundle deflection, or AV nodal conduction time, HV = conduction time through the His bundle and the bundle branch-Purkinje system.

Renal Function
There is a transient increase in electrolyte excretion, including sodium. Nicardipine does not cause generalized fluid retention, as measured by weight changes, although 7 to 8% of the patients experience pedal edema.

Effects in Angina Pectoris
In controlled clinical trials of up to 12 weeks duration in patients with chronic stable angina, nicardipine increased exercise tolerance and reduced nitroglycerin consumption and the frequency of anginal attacks. The antianginal efficacy of nicardipine hydrochloride (20 to 40 mg) has been demonstrated in four placebo-controlled studies involving 258 patients with chronic stable angina. In exercise tolerance testing, nicardipine significantly increased time to angina, total exercise duration and time to 1 mm ST segment depression. Included among these four studies was a dose-definition study in which dose-related improvements in exercise tolerance at one and four hours post-dosing and reduced frequency of anginal attacks were seen at doses of 10, 20 and 30 mg TID. Effectiveness at 10 mg TID was, however, marginal. In a fifth placebo-controlled study, the antianginal efficacy of nicardipine was demonstrated at 8 hours post-dose (trough). The sustained efficacy of nicardipine has been demonstrated over long-term dosing. Blood pressure fell in patients with angina by about 10/8 mmHg at peak blood levels and was little different from placebo at trough blood levels.

Effects in Hypertension
Nicardipine produced dose-related decreases in both systolic and diastolic blood pressure in clinical trials. The antihypertensive efficacy of nicardipine administered three times daily has been demonstrated in three placebo-controlled studies involving 517 patients with mild to moderate hypertension. The blood pressure responses in the three studies were statistically significant from placebo at peak (1 hour post-dosing) and trough (8 hours post-dosing) although it is apparent that well over half of the antihypertensive effect is lost by the end of the dosing interval. The results from placebo controlled studies of nicardipine given three times daily are shown in the following table:

	SYSTOLIC BP (mmHg)			DIASTOLIC BP (mmHg)		
	Number of	Mean Peak	Mean Trough	Number of	Mean Peak	Mean Trough

conduction time through the His bundle and the bundle branch-Purkinje system.

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	SYSTOLIC BP (mmHg)					DIASTOLIC BP (mmHg)			
Dose	Number of Patients	Mean Peak Response	Mean Trough Response	Trough/ Peak	Dose	Number of Patients	Mean Peak Response	Mean Trough Response	Trough/ Peak
20 mg	50	-10.3	-4.9	48%	20 mg	50	-10.6	-4.6	43%
	52	-17.6	-7.9	45%		52	-9.0	-2.9	32%
30 mg	45	-14.5	-7.2	50%	30 mg	45	-12.8	-4.9	38%
	44	-14.6	-7.5	51%		44	-14.2	-4.3	30%
40 mg	50	-16.3	-9.5	58%	40 mg	50	-15.4	-5.9	38%
	38	-15.9	-6.0	38%		38	-14.8	-3.7	25%

The responses are shown as differences from the concurrent placebo control group. The large changes between peak and trough effects were not accompanied by observed side effects at peak response times. In a study using 24 hour intra-arterial blood pressure monitoring, the circadian variation in blood pressure remained unaltered, but the systolic and diastolic blood pressures were reduced throughout the whole 24 hours.

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

INDICATIONS AND USAGE

I. Stable Angina
Nicardipine hydrochloride capsules are indicated for the management of patients with chronic stable angina (effort-associated angina). Nicardipine hydrochloride capsules may be used alone or in combination with beta-blockers.

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

CONTRAINDICATIONS

Nicardipine hydrochloride is contraindicated in patients with hypersensitivity to the drug.

Because part of the effect of nicardipine is secondary to reduced afterload, the drug is also contraindicated in patients with advanced aortic stenosis. Reduction of diastolic pressure in these patients may worsen rather than improve myocardial oxygen balance.

WARNINGS

Increased Angina
About 7% of patients in short term placebo-controlled angina trials have developed increased frequency, duration or severity of angina on starting nicardipine or at the time of dosage increases, compared with 4% of patients on placebo. Comparisons with beta-blockers also show a greater frequency of increased angina, 4% vs 1%. The mechanism of this effect has not been established. (See ADVERSE REACTIONS.)

Use in Patients with Congestive Heart Failure
Although preliminary hemodynamic studies in patients with congestive heart failure have shown that nicardipine reduced afterload without impairing myocardial contractility, it has a negative inotropic effect *in vitro* and in some patients. Caution should be exercised when using the drug in congestive heart failure patients, particularly in combination with a beta-blocker.

Beta-Blocker Withdrawal
Nicardipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker, preferably over 8 to 10 days.

PRECAUTIONS

General
Blood Pressure: Because nicardipine decreases peripheral resistance, careful monitoring of blood pressure during the initial administration and titration of nicardipine is suggested. Nicardipine, like other calcium channel blockers, may occasionally produce symptomatic hypotension. Caution is advised to avoid systemic hypotension when administering the drug to patients who have sustained an acute cerebral infarction or hemorrhage. Because of prominent effects at the time of peak blood levels, initial titration should be performed with measurements of blood pressure at peak effect (1 to 2 hours after dosing) and just before the next dose.

Use in patients with impaired hepatic function: Since the liver is the major site of biotransformation and nicardipine is subject to first pass metabolism, the drug should be used with caution in patient having impaired liver function or reduced hepatic blood flow. Patients with severe liver disease developed elevated blood levels (4-fold increase in AUC) and prolonged half-life (19 hours) of nicardipine. (See DOSAGE AND ADMINISTRATION.)

Use in patients with impaired renal function: When nicardipine hydrochloride capsules 20 mg or 30 mg TID were given to hypertensive patients with mild renal impairment, mean plasma concentrations, AUC, and Cmax were approximately 2-fold higher in renally impaired patients than in healthy controls. Doses in these patients must be adjusted. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

Drug Interactions
Beta-Blockers
In controlled clinical studies, adrenergic beta-receptor blockers have been frequently administered concomitantly with nicardipine hydrochloride capsules. The combination is well tolerated.

Cimetidine
Cimetidine increases nicardipine plasma levels. Patients receiving the two drugs concomitantly should be carefully monitored.

Digoxin
Some calcium blockers may increase the concentration of digitalis preparations in the blood. Nicardipine usually does not alter the plasma levels of digoxin, however, serum digoxin levels should be evaluated after concomitant therapy with nicardipine hydrochloride is initiated.

Aluminum and Magnesium Hydroxides
Co-administration of an antacid containing 600 mg aluminum hydroxide and 300 mg magnesium hydroxide had no effect on nicardipine absorption.

Fentanyl Anesthesia
Severe hypotension has been reported during fentanyl anesthesia with concomitant use of a beta-blocker and a calcium channel blocker. Even though such interactions were not seen during clinical studies with nicardipine, an increased volume of circulating fluids might be required if such an interaction were to occur.

Cyclosporine
Concomitant administration of nicardipine and cyclosporine results in elevated plasma cyclosporine levels. Plasma concentrations of cyclosporine should therefore be closely monitored, and its dosage reduced accordingly, in patients treated with nicardipine.

When therapeutic concentrations of *furosemide, propranolol, dipyridamole, warfarin, quinidine,* or *naproxen* were added to human plasma *(in vitro)*, the plasma protein binding of nicardipine was not altered.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Rats treated with nicardipine in the diet (at concentrations calculated to provide daily dosage levels of 5, 15, or 45 mg/kg/day) for two years showed a dose-dependent increase in thyroid hyperplasia and neoplasia (follicular adenoma/carcinoma). One and three month studies in the rat have suggested that these results are linked to a nicardipine-induced reduction in plasma thyroxine (T4) levels with a consequent increase in plasma levels of thyroid stimulating hormone (TSH). Chronic elevation of TSH is known to cause hyperstimulation of the thyroid. In rats on an iodine deficient diet, nicardipine administration for one month was associated with thyroid hyperplasia that was prevented by T4 supplementation. Mice treated with nicardipine in the diet (at concentrations calculated to provide daily dosage levels of up to 100 mg/kg/day) for up to 18 months showed no evidence of neoplasia of any tissue and no evidence of thyroid changes. There was no evidence of thyroid pathology in dogs treated with up to 25 mg nicardipine/kg/day for one year and no evidence of effects of nicardipine on thyroid function (plasma T4 and TSH) in man.

There was no evidence of a mutagenic potential of nicardipine in a battery of genotoxicity tests conducted on microbial indicator organisms, in micronucleus tests in mice and hamsters, or in a sister chromatid exchange study in hamsters.

No impairment of fertility was seen in male or female rats administered nicardipine at oral doses as high as 100 mg/kg/day (50 times the 40 mg TID maximum recommended antianginal or antihypertensive dose in man, assuming a patient weight of 60 kg).

Pregnancy Pregnancy Category C
Nicardipine was embryocidal when administered orally to pregnant Japanese White rabbits, during organogenesis, at 150 mg/kg/day (a dose associated with marked body weight gain suppression in the treated doe) but not at 50 mg/kg/day (25 times the maximum recommended antianginal or antihypertensive dose in man). No adverse effects on the fetus were observed when New Zealand albino rabbits were treated, during organogenesis, with up to 100 mg nicardipine/kg/day (a dose associated with significant mortality in the treated doe). In pregnant rats administered nicardipine orally at up to 100 mg/kg/day (50 times the maximum recommended human dose) there was no evidence of embryolethality or teratogenicity. However, dystocia, reduced birth weights, reduced neonatal survival and reduced neonatal weight gain were noted. There are no adequate and well-controlled studies in pregnant women. Nicardipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Studies in rats have shown significant concentrations of nicardipine in maternal milk following oral administration. For this reason it is recommended that women who wish to breast-feed should not take this drug.

Pediatric Use
Safety and efficacy in patients under the age of 18 have not been established.

Use in the Elderly
Pharmacokinetic parameters did not differ between elderly hypertensive patients (≥65 years) and healthy controls after one week of nicardipine hydrochloride treatment at 20 mg TID. Plasma nicardipine concentrations in elderly hypertensive patients were similar to plasma concentrations in healthy young adult subjects when nicardipine hydrochloride was administered at doses of 10, 20 and 30 mg TID, suggesting that the pharmacokinetics of nicardipine are similar in young and elderly hypertensive patients. No significant differences in responses to nicardipine have been observed in elderly patients and the general adult population of patients who participated in clinical studies.

ADVERSE REACTIONS

In multiple-dose U.S. and foreign controlled short-term (up to three months) studies 1,910 patients received nicardipine alone or in combination with other drugs. In these studies adverse events were reported spontaneously; adverse experiences were generally not serious but occasionally required dosage adjustment and about 10% of patients left the studies prematurely because of them. Peak responses were not observed to be associated with adverse effects during clinical trials, but physicians should be aware that adverse effects associated with decreases in blood pressure (tachycardia, hypotension, etc.) could occur around the time of the peak effect. Most adverse effects were expected consequences of the vasodilator effects of nicardipine.

Angina
The incidence rates of adverse effects in anginal patients were derived from multicenter, controlled clinical trials. Following are the rates of adverse effects for nicardipine (N=520) and placebo (N=310), respectively, that occurred in 0.4% of patients or more. These represent events considered probably drug-related by the investigator (except for certain cardiovascular events which were recorded in a different category). Where the frequency of adverse effects for nicardipine and placebo is similar, causal relationship is uncertain. The only dose-related effects were pedal edema and increased angina.

Percent of Patients with Adverse Effects in Controlled Studies
(Incidence of discontinuations shown in parentheses)

Adverse Experience	Nicardipine (N= 520)	PLACEBO (N= 310)
Pedal Edema	7.1 (0)	0.3 (0)
Dizziness	6.9 (1.2)	0.6 (0)
Headache	6.4 (0.6)	2.6 (0)
Asthenia	5.8 (0.4)	2.6 (0)
Flushing	5.6 (0.4)	1.0 (0)
Increased Angina	5.6 (3.5)	4.2 (1.9)
Palpitations	3.3 (0.4)	0.0 (0)
Nausea	1.9 (0)	0.3 (0)
Dyspepsia	1.5 (0.6)	0.6 (0.3)
Dry Mouth	1.4 (0)	0.3 (0)
Somnolence	1.4 (0)	1.0 (0)
Rash	1.2 (0.2)	0.3 (0)
Tachycardia	1.2 (0.2)	0.6 (0)
Myalgia	1.0 (0)	0.0 (0)
Other edema	1.0 (0)	0.0 (0)
Paresthesia	1.0 (0.2)	0.3 (0)
Sustained Tachycardia	0.8 (0.6)	0.0 (0)
Syncope	0.8 (0.2)	0.0 (0)
Constipation	0.6 (0.2)	0.6 (0)
Dyspnea	0.6 (0)	0.0 (0)
Abnormal ECG	0.6 (0.6)	0.0 (0)
Malaise	0.6 (0)	0.0 (0)
Nervousness	0.6 (0)	0.3 (0)
Tremor		0.0 (0)

In addition, adverse events were observed which are not readily distinguishable from the natural history of the atherosclerotic vascular disease in these patients. Adverse events in this category each occurred in <0.4% of patients receiving nicardipine and included myocardial infarction, atrial fibrillation, exertional hypotension, pericarditis, heart block, cerebral ischemia and ventricular tachycardia. It is possible that some of these events were drug-related.

Hypertension
The incidence rates of adverse effects in hypertensive patients were derived from multicenter, controlled clinical trials. Following are the rates of adverse effects for nicardipine (N= 1390) and placebo (N= 211), respectively, that occurred in 0.4% of patients or more. These represent events considered probably drug-related by the investigator. Where the frequency of adverse effects for nicardipine and placebo is similar, causal relationship is uncertain. The only dose-related effect was pedal edema.

Percent of Patients with Adverse Effects in Controlled Studies
(Incidence of discontinuations shown in parentheses)

Adverse Experience	Nicardipine (N = 1390)	PLACEBO (N = 211)
Flushing	9.7 (2.1)	2.8 (0)
Headache	8.2 (2.6)	4.7 (0)
Pedal Edema	8.0 (1.8)	0.9 (0)
Asthenia	4.2 (1.7)	0.5 (0)
Palpitations	4.1 (1.0)	0.0 (0)
Dizziness	4.0 (1.8)	0.0 (0)
Tachycardia	3.4 (1.2)	0.5 (0)
Nausea	2.2 (0.9)	0.9 (0)
Somnolence	1.1 (0.1)	0.0 (0)
Dyspepsia	0.8 (0.3)	0.5 (0)
Insomnia	0.6 (0.1)	0.0 (0)
Malaise	0.6 (0.1)	0.0 (0)
Other edema	0.6 (0.3)	1.4 (0)
Abnormal dreams	0.4 (0)	0.0 (0)
Dry mouth	0.4 (0.1)	0.0 (0)
Nocturia	0.4 (0)	0.0 (0)
Rash	0.4 (0.4)	0.0 (0)
Vomiting	0.4 (0.4)	0.0 (0)

Rare Events
The following rare adverse events have been reported in clinical trials or the literature:

Body as a Whole: infection, allergic reaction
Cardiovascular: hypotension, postural hypotension, atypical chest pain, peripheral vascular disorder, ventricular extrasystoles, ventricular tachycardia
Digestive: sore throat, abnormal liver chemistries
Musculoskeletal: arthralgia
Nervous: hot flashes, vertigo, hyperkinesia, impotence, depression, confusion, anxiety
Respiratory: rhinitis, sinusitis
Special Senses: tinnitus, abnormal vision, blurred vision
Urogenital: increased urinary frequency

OVERDOSAGE

Overdosage with a 600 mg single dose (15 to 30 times normal clinical dose) has been reported. Marked hypotension (blood pressure unobtainable) and bradycardia (heart rate 20 bpm in normal sinus rhythm) occurred, along with drowsiness, confusion and slurred speech. Supportive treatment with a vasopressor resulted in gradual improvement with normal vital signs approximately 9 hours post treatment.

Based on results obtained in laboratory animals, overdosage may cause systemic hypotension, bradycardia (following initial tachycardia) and progressive [illegible] and sporadic focal hepatic necrosis were noted in some animal species receiving very

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Other edema	0.6 (0.3)	1.4 (0)
Abnormal dreams	0.4 (0)	0.0 (0)
Dry mouth	0.4 (0.1)	0.0 (0)
Nocturia	0.4 (0)	0.0 (0)
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Based on results obtained in laboratory animals, overdosage may cause systemic hypotension, bradycardia (following initial tachycardia) and progressive atrioventricular conduction block. Reversible hepatic function abnormalities and sporadic focal hepatic necrosis were noted in some animal species receiving very large doses of nicardipine.

For treatment of overdose standard measures (for example, evacuation of gastric contents, elevation of extremities, attention to circulating fluid volume and urine output) including monitoring of cardiac and respiratory functions should be implemented. The patient should be positioned so as to avoid cerebral anoxia. Frequent blood pressure determinations are essential. Vasopressors are clinically indicated for patients exhibiting profound hypotension. Intravenous calcium gluconate may help reverse the effects of calcium entry blockade.

DOSAGE AND ADMINISTRATION

Angina
The dose should be individually titrated for each patient beginning with 20 mg three times daily. Doses in the range of 20 to 40 mg three times a day have been shown to be effective. At least three days should be allowed before increasing the nicardipine hydrochloride dose to ensure achievement of steady state plasma drug concentrations.

Concomitant Use With Other Antianginal Agents
1. Sublingual NTG may be taken as required to abort acute anginal attacks during nicardipine therapy.
2. Prophylactic Nitrate Therapy- nicardipine may be safely coadministered with short- and long-acting nitrates
3. Beta-blockers- nicardipine may be safely coadministered with beta-blockers. (See PRECAUTIONS, Drug Interactions.)

Hypertension
The dose of nicardipine hydrochloride should be individually adjusted according to the blood pressure response beginning with 20 mg three times daily. The effective doses in clinical trials have ranged from 20 mg to 40 mg three times daily. The maximum blood pressure lowering effect occurs approximately 1 to 2 hours after dosing. **To assess the adequacy of blood pressure response, the blood pressure should be measured at trough (8 hours after dosing). Because of the prominent peak effects of nicardipine, blood pressure should be measured 1 to 2 hours after dosing, particularly during initiation of therapy.** (See PRECAUTIONS: Blood pressures, INDICATIONS AND USAGE, CLINICAL PHARMACOLOGY, Effects in Hypertension.) At least three days should be allowed before increasing the nicardipine dose to ensure achievement of steady state plasma drug concentrations.

Concomitant use with other Antihypertensive Agents
1. Diuretics- nicardipine may be safely coadministered with thiazide diuretics.
2. Beta-blockers- nicardipine may be safely coadministered with beta-blockers. (See PRECAUTIONS, Drug Interactions.)

Special Patient Populations
Renal Insufficiency - although there is no evidence that nicardipine impairs renal function, careful dose titration beginning with 20 mg TID is advised. (See PRECAUTIONS.)

Hepatic Insufficiency - nicardipine should be administered cautiously in patients with severely impaired hepatic function. A suggested starting dose of 20 mg twice a day is advised with individual titration based on clinical findings maintaining the twice a day schedule. (See PRECAUTIONS.)

Congestive Heart Failure - Caution is advised when titrating nicardipine dosage in patients with congestive heart failure. (See WARNINGS.)

HOW SUPPLIED

Nicardipine hydrochloride 20 mg capsules are available in opaque white/light blue hard gelatin capsules printed "G" on the cap and "0041" on the capsule body. These are supplied in bottles of 100 (NDC 55567-041-18), bottles of 500 (NDC 55567-041-25) and in cartons of 100 unit dose blister packages (NDC 55567-041-06).

Nicardipine hydrochloride 30 mg capsules are available in opaque light blue hard gelatin capsules printed "G" on the cap and "0042" on the capsule body. These are supplied in bottles of 100 (NDC 55567-042-18), bottles of 500 (NDC 55567-042-25) and in cartons of 100 unit dose blister packages (NDC 55567-042-06).

Store bottles at room temperature between 15° and 30°C (59° and 86°F) and dispense in tight, light-resistant containers.

Store blister packages at room temperature between 15° and 30°C (59° and 86°F) and protect from excessive humidity and light. To protect from light, product should remain in manufacture's package until consumed.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by:
GENPHARM INC.
Toronto, Canada
M8Z 2S6
1-800-661-7134

Revised August 1997

003-168 REV.#01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74928

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3

2. ANDA 74-928

3. NAME AND ADDRESS OF APPLICANT
Genpharm Inc.
37 Advance Road
Etobicoke, Ontario
Canada M8Z 2S6

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.
- 10/23/96 - O/NC, Bio. information.
- 1/3/97 - O/NC, Bio. information.
- 3/12/97 - O/NC, response to Bio. letter.
- 6/4/97 - Response to 1st def. letter (chem. & labeling).
- 6/25/97 - O/NC, Bio. phone amendment.
- 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.
- 8/4/97 - 2nd def. Facsimile (chem. & labeling).
- 8/26/97 - 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
℞

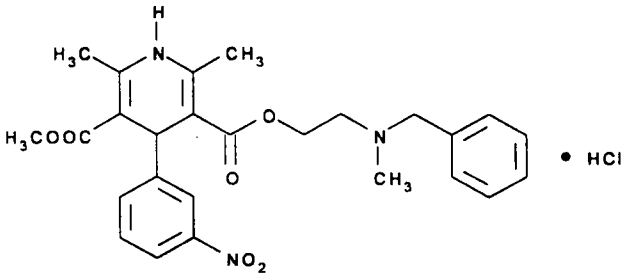
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Capsule

14. POTENCY
20 mg & 30 mg

15. CHEMICAL NAME AND STRUCTURE

Nicardipine Hydrochloride
$C_{26}H_{29}N_3O_6.HCl$; M.W. = 515.99



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