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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NICARDIPINE HYDROCHLORIDE IN SODIUM CHLORIDE INJECTION safely and effectively. See full prescribing information for NICARDIPINE HYDROCHLORIDE IN SODIUM CHLORIDE INJECTION.

NICARDIPINE HYDROCHLORIDE IN SODIUM CHLORIDE injection, for intravenous use
Initial U.S. Approval: 1988

RECENT MAJOR CHANGES	11/2024
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INDICATIONS AND USAGE

Nicardipine hydrochloride in 0.9% sodium chloride injection is a calcium channel blocker indicated for the short-term treatment of hypertension when oral therapy is not feasible.

DOSAGE AND ADMINISTRATION

- Individualize dosage based upon the severity of hypertension and response of the patient during dosing (2.1).
- When substituting for oral nicardipine therapy, use the intravenous infusion rate as follows (2.3):

Oral Nicardipine Dose	Equivalent Intravenous Infusion Rate
20 mg every 8 hours	0.5 mg/hr
30 mg every 8 hours	1.2 mg/hr
40 mg every 8 hours	2.2 mg/hr

- In a drug-free patient, initiate therapy at 5 mg/hr. Increase the infusion rate by 2.5 mg/hr to a maximum of 15 mg/hr until desired blood pressure reduction is achieved. For a gradual blood pressure reduction the rate can be increased every 15 minutes, for a rapid reduction, every 5 minutes (2.4).
- If hypotension or tachycardia ensues, discontinue the infusion. After stabilized, patient can be restarted at low doses such as 3 mg/hr to 5 mg/hr (2.5).

DOSAGE FORMS AND STRENGTHS

- 20 mg nicardipine hydrochloride in 200 mL 0.9 % sodium chloride injection (0.1 mg/mL) in a single dose container (3)

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FULL PRESCRIBING INFORMATION:

1. INDICATIONS AND USAGE

1.1 Hypertension

Nicardipine hydrochloride in 0.9% sodium chloride injection is indicated for the short-term treatment of hypertension when oral therapy is not feasible or desirable. For prolonged control of blood pressure, transfer patients to oral medication as soon as their clinical condition permits (See Dosage and Administration (2.6)).

2. DOSAGE AND ADMINISTRATION

2.1 General Information

Individualize dosing based on the severity of hypertension and the response of the patient during dosing. Monitor blood pressure and heart rate both during and after the infusion to avoid tachycardia or too rapid or excessive reduction in either systolic or diastolic blood pressure.

Administer nicardipine hydrochloride in 0.9% sodium chloride injection by slow continuous infusion by a central line or through a large peripheral vein. Change the infusion site every 12 hours if administered via peripheral vein (See Intravenous Infusion Site (5.7)).

2.2 Inspection and Preparation

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Do not use the solution if particulate matter, precipitate, or crystallization is present, or if the container appears damaged.

Single Dose Containers

Discard the container for nicardipine hydrochloride in 0.9% sodium chloride injection.

Check the requirements for minute leaks prior to use; ensure that the seal is intact. If leaks are found, discard solution as sterility may be impaired.

Do not combine nicardipine hydrochloride in 0.9% sodium chloride injection with any product in the same intravenous line or premixed container. Do not add supplementary medication to the bag. Protect from light until ready to use.

Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before the administration of the fluid from the secondary container is complete.

Discard unused Portion

Preparation for administration

- Suspend container from eyellet support.
- Remove protector from outlet port at bottom of container.
- Attach administration set. Refer to complete directions accompanying set.

2.3 Dosage as a Substitute for Oral Nicardipine Therapy

The intravenous infusion rate required to produce an average plasma concentration equivalent to a given oral dose at steady state is shown in the following table:

Oral Nicardipine Dose	Equivalent Intravenous Infusion Rate
20 mg every 8 hours	0.5 mg/hr
30 mg every 8 hours	1.2 mg/hr
40 mg every 8 hours	2.2 mg/hr

2.4 Dosage for Initiation of Therapy in a Drug-Free Patient

The time course of blood pressure decrease is dependent on the initial rate of infusion and the frequency of dosage adjustment. Nicardipine hydrochloride in 0.9% sodium chloride injection is administered by slow continuous infusion at a concentration of 0.1 mg/mL. With constant infusion, blood pressure begins to fall within minutes. It reaches about 50% of its ultimate decrease in about 45 minutes.

When treating acute hypertensive episodes in patients with chronic hypertension, discontinuation of infusion is followed by a 50% offset of action in 30 minutes plus minus 7 minutes but plasma levels of drug and gradually decreasing antihypertensive effects exist for many hours.

Titration

For a gradual reduction in blood pressure, initiate therapy at a rate of 5 mg/hr. If desired blood pressure reduction is not achieved at this dose, increase the infusion rate by 2.5 mg/hr every 15 minutes up to a maximum of 15 mg/hr, until desired blood pressure reduction is achieved. For more rapid blood pressure reduction, titrate every 5 minutes.

Maintenance

Adjust the rate of infusion as needed to maintain desired responses.

2.5 Conditions Requiring Infusion Adjustment

Hypotension or Tachycardia: In case of hypotension or tachycardia, discontinue infusion. When blood pressure and heart rate stabilize, restart infusion at low doses such as 30 mL/hr to 50 mL/hr (3 mg/hr to 5 mg/hr) and titrate to maintain desired blood pressure.

Infusion Site Changes: Change infusion site every 12 hours if administered via peripheral vein.

Impaired Cardiac, Hepatic, or Renal Function: Monitor closely when titrating nicardipine hydrochloride in 0.9% sodium chloride injection in patients with congestive heart failure or impaired hepatic or renal function (See Warnings and Precautions (5.4, 5.5 and 5.6)).

2.6 Transfer to Oral Antihypertensive Agents

If treatment includes transfer to an oral antihypertensive agent other than nicardipine capsules, initiate oral therapy upon discontinuation of nicardipine hydrochloride in 0.9% sodium chloride injection.

When switching to a three times a day regimen of nicardipine capsules, administer the first dose 1 hour prior to discontinuation of the infusion.

3. DOSAGE FORMS AND STRENGTHS

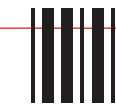
Nicardipine hydrochloride in 0.9% sodium chloride injection is a clear colorless to yellow solution and is available in the following presentations:

- 20 mg nicardipine hydrochloride in 200 mL 0.9% sodium chloride injection (0.1 mg/mL) in a single dose container.
- 40 mg nicardipine hydrochloride in 200 mL 0.9% sodium chloride injection (0.2 mg/mL) in a single dose container

4. CONTRAINDICATIONS

4.1 Advanced Aortic Stenosis

Do not use nicardipine in patients with advanced aortic stenosis because of the afterload reduction effect of nicardipine. Reduction of diastolic pressure in these patients may worsen rather than improve myocardial oxygen balance.



- 40 mg nicardipine hydrochloride in 200 mL 0.9 % sodium chloride injection (0.2 mg/mL) in a single dose container (3)

CONTRAINDICATIONS

- Do not use in patients with advanced aortic stenosis (4.1).

WARNINGS AND PRECAUTIONS

- To reduce the possibility of venous thrombosis, phlebitis, and vascular impairment, do not use small veins, such as those on the dorsum of the hand or wrist. Avoid intraarterial administration or extravasation (5.7).
- To minimize the risk of peripheral venous irritation, change the site of infusion of nicardipine every 12 hours (5.7).
- Nicardipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal. Withdraw beta-blockers gradually (5.8).
- Closely monitor response in patients with angina (5.3), congestive heart failure (5.4), impaired hepatic function (5.5), portal hypertension (5.5), and renal impairment (5.6) and pheochromocytoma (5.9).

ADVERSE REACTIONS

Most common adverse reactions are headache (13%), hypotension (5%), tachycardia (4%) and nausea/vomiting (4%).

To report SUSPECTED ADVERSE REACTIONS, contact Cipla Ltd. at 1-866-604-3288 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Cimetidine increases nicardipine plasma levels (7.3).
- Nicardipine may increase cyclosporine and tacrolimus plasma levels. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended when co-administering nicardipine. (7.5, 7.6).

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1).
- Nursing Mothers: It is recommended that women who wish to breastfeed should not be given this drug (8.3).
- Safety and efficacy in patients under the age of 18 have not been established (8.4).

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7. DRUG INTERACTIONS

- Antihypertensive Agents
- Beta-Blockers
- Cimetidine
- Digoxin
- Cyclosporine
- Tacrolimus
- In Vitro Interaction

8. USE IN SPECIFIC POPULATIONS

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16. HOW SUPPLIED/STORAGE AND HANDLING

- How Supplied
- Storage and Handling

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

5. WARNINGS AND PRECAUTIONS

5.1 Excessive Pharmacologic Effects

In administering nicardipine, close monitoring of blood pressure and heart rate is required. Nicardipine may occasionally produce symptomatic hypotension or tachycardia. Avoid systemic hypotension when administering the drug to patients who have sustained an acute cerebral infarction or hemorrhage.

5.2 Rapid Decreases in Blood Pressure

No clinical cases have been reported suggestive of a too rapid decrease in blood pressure with nicardipine. However, as with any antihypertensive agent, blood pressure lowering should be accomplished over as long a time as is compatible with the patient's clinical status.

5.3 Use in Patients with Angina

Increases in frequency, duration, or severity of angina have been seen in chronic oral therapy with nicardipine capsules. Induction or exacerbation of angina has been seen in less than 1% of coronary artery disease patients treated with nicardipine. The mechanism of this effect has not been established.

5.4 Use in Patients with Congestive Heart Failure

Nicardipine reduced afterload without impairing myocardial contractility in preliminary hemodynamic studies in CHF patients. However, *in vitro* and in some patients, a negative inotropic effect has been observed. Therefore, monitor vital signs carefully when using nicardipine, particularly in combination with a beta-blocker, in patients with CHF or significant left ventricular dysfunction.

5.5 Use in Patients with Impaired Hepatic Function

Since nicardipine is metabolized in the liver, consider lower dosages and closely monitor response. Nicardipine administered intravenously increased hepatic venous pressure gradient by 4 mmHg in cirrhotic patients at high doses (5 mg/20 min) in open study. Use caution in patients with portal hypertension.

5.6 Use in Patients with Impaired Renal Function

When nicardipine was given to mild-to-moderate hypertensive patients with moderate renal impairment, a significantly lower systemic clearance and higher AUC was observed. These results are consistent with those seen after oral administration of nicardipine. Careful dose titration is advised when treating patients with more than mild renal impairment.

5.7 Intravenous Infusion Site

To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, extravasation, and the rare occurrence of vascular impairment, administer drug through large peripheral veins or central veins rather than arteries or small peripheral veins, such as those on the dorsum of the hand or wrist. To minimize the risk of peripheral venous irritation, consider changing the site of the drug infusion every 12 hours.

5.8 Beta-Blocker Withdrawal

Nicardipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal. Withdraw beta-blockers gradually.

5.9 Use in Patients with Pheochromocytoma

Only limited clinical experience exists in use of nicardipine for patients with hypertension from pheochromocytoma.

6. ADVERSE REACTIONS

6.1 Adverse Reactions Observed in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the risks observed in practice.

Two hundred forty-four patients participated in two multicenter, double-blind, placebo-controlled trials of nicardipine. Adverse experiences were generally not serious and most were expected consequences of vasodilation. Adverse reactions occasionally required dosage adjustment. Therapy was discontinued in approximately 12% of patients, mainly due to hypotension, headache, and tachycardia. Adverse reactions that occurred more often on nicardipine than on placebo by at least 2% were headache (13%) and nausea/vomiting (4%).

The following adverse reactions have been reported in clinical trials or in the literature during the use of intravenously administered nicardipine.

Body as a Whole: fever, neck pain

Cardiovascular: angina pectoris, atrioventricular block, ST segment depression, inverted T wave, deep-vein thrombophlebitis

Digestive: dyspepsia

Hemic and Lymphatic: thrombocytopenia

Metabolic and Nutritional: hypophosphatemia, peripheral edema

Nervous: confusion, hypotonia

Respiratory: respiratory disorder

Special Senses: conjunctivitis, ear disorder, tinnitus

Urogenital: urinary frequency

Sinus node dysfunction and myocardial infarction, which may be due to disease progression, have been seen in patients on chronic therapy with orally administered nicardipine.

7. DRUG INTERACTIONS

7.1 Antihypertensive Agents

Since nicardipine hydrochloride injection may be administered to patients already being treated with other medications, including other antihypertensive agents, careful monitoring of these patients is necessary to detect and to treat promptly any undesired effects from concomitant administration.

7.2 Beta-Blockers

In most patients, nicardipine hydrochloride injection can safely be used concomitantly with beta-blockers. However, monitor response carefully when combining nicardipine hydrochloride injection with a beta-blocker in the treatment of congestive heart failure patients (See Warnings and Precautions (5.4)).

7.3 Cimetidine

Cimetidine has been shown to increase nicardipine plasma concentrations with oral nicardipine administration. Carefully monitor patients receiving the two drugs concomitantly. Data with other histamine-2 antagonists are not available.

7.4 Digoxin

Studies have shown that oral nicardipine usually does not alter digoxin plasma concentrations.

7.5 Cyclosporine

Concomitant administration of oral or intravenous nicardipine and cyclosporine results in elevated plasma cyclosporine levels through nicardipine inhibition of hepatic microsomal enzymes, including CYP3A4. Monitor closely plasma concentrations of cyclosporine during nicardipine hydrochloride injection administration, and adjust the dose of cyclosporine accordingly.

7.5 Tacrolimus

Concomitant administration of intravenous nicardipine and tacrolimus may result in elevated plasma tacrolimus levels through nicardipine inhibition of hepatic microsomal enzymes, including CYP3A4. Closely monitor plasma concentrations of tacrolimus during nicardipine administration, and adjust the dose of tacrolimus accordingly.

7.7 In Vitro Interaction

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

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There are no adequate and well-controlled studies of nicardipine use in pregnant women. There are limited human data in pregnant women with pre-eclampsia and preterm labor. In animal reproduction and developmental toxicity studies, evidence of fetal harm was observed. Therefore use nicardipine during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In reproduction studies conducted in rats and rabbits, increased embryolethality occurred when nicardipine was administered intravenously at doses equivalent to human intravenous doses of 1.6 (rats) and 0.32 mg/kg/day (rabbits).

Increased embryolethality was also observed when nicardipine was administered orally to pregnant rabbits at a dose equivalent to a human oral dose of about 48 mg/kg/day (a dose 24 times the maximum recommended human oral dose and one associated with marked maternal body weight gain suppression). At a lower oral dose, equivalent to a human dose of about 32 mg/kg/day (16 times the maximum recommended human oral dose), in a different strain of rabbit, there were no adverse effects on the fetus, though there was increased maternal mortality. There was no evidence of embryolethality or teratogenicity when pregnant rats were administered nicardipine orally at a dose equivalent to a human oral dose of about 16 mg/kg/day (8 times the MRHD); however, dystocia, reduced birth weight, reduced neonatal survival and reduced neonatal weight gain were reported (see Nonclinical Toxicology (13.1)).

8.3 Nursing Mothers

Nicardipine is minimally excreted into human milk. Among 18 infants exposed to nicardipine through breast milk in the postpartum period, calculated daily infant dose was less than 0.3 mcg and there were no adverse events observed. It is recommended that women who wish to breastfeed should not be given this drug.

In a study of 11 women who received oral nicardipine 4 days to 14 days postpartum, 4 women received immediate-release nicardipine 40 to 80 mg daily, 6 women received sustained-release nicardipine 100 mg to 150 mg daily, and one woman received intravenous nicardipine 120 mg daily. The peak milk concentration was 7.3 mcg/L (range 1.9 to 18.8), and the mean milk concentration was 4.4 mcg/L (range 1.3 to 13.8).

Infants received an average of 0.073% of the weight-adjusted maternal oral dose and 0.14% of the weight-adjusted maternal intravenous dose.

In another study of seven women who received intravenous nicardipine for an average of 1.9 days in the immediate postpartum period, therapy for pre-eclampsia, 34 milk samples were obtained at unspecified times and nicardipine was undetectable in 26 of 34 (76%) of the samples. Four women who received 1 to 6.5 mg/hour of nicardipine had 6 milk samples with detectable nicardipine levels (range 5.1 to 18.5 mcg/L). The highest concentration of 18.5 mcg/L was found in a woman who received 5.5 mg/hour of nicardipine. The estimated maximum dose in a breastfed infant was less than 0.3 mcg daily or 0.015% to 0.004% of the therapeutic dose in a 1 kg infant.

8.4 Pediatric Use

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

8.5 Geriatric Use

The steady-state pharmacokinetics of nicardipine are similar in elderly hypertensive patients (greater than 65 years) and young healthy adults.

Clinical studies of nicardipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and concomitant disease of other drug therapy.

10. OVERDOSAGE

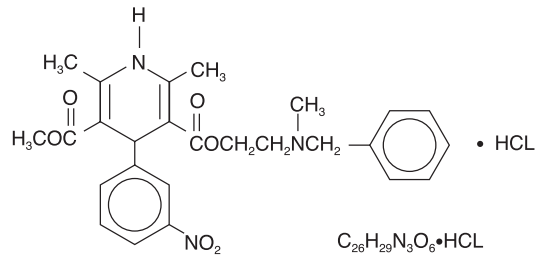
Several overdoses with orally administered nicardipine have been reported. One adult patient allegedly ingested 600 mg of nicardipine immediate release capsules, and another patient, 2160 mg of the sustained release formulation of nicardipine. Symptoms included marked hypotension, bradycardia, palpitations, flushing, drowsiness, confusion and slurred speech. All symptoms resolved without sequelae. An overdose occurred in a one-year-old child who ingested half of the powder in a 30 mg nicardipine standard capsule. The child remained asymptomatic.

Based on results obtained in laboratory animals, lethal overdose 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 including monitoring of cardiac and respiratory functions should be implemented. The patient should be positioned 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.

11. DESCRIPTION

Nicardipine hydrochloride is a calcium ion inhibitor (slow channel blocker or calcium channel blocker). Nicardipine hydrochloride is a dihydropyridine derivative with 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 has the following structure:



Nicardipine hydrochloride is a pale greenish yellow powder that has a melting point range of 167-171°C. It is insoluble in methanol and acetic acid; sparingly soluble in ethanol, slightly soluble in water. It has a molecular weight of 515.99.

Nicardipine hydrochloride in 0.9% sodium chloride injection is available as a single-use, ready-to-use, iso-osmotic, clear, colorless to yellow solution for intravenous administration in a 200 mL single dose container. Each mL contains 0.1 mg of 0.2 mg nicardipine hydrochloride USP in 0.9% sodium chloride, USP. Hydrochloric acid (q.s.) may have been added to adjust pH to 3.5 to 4.7.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nicardipine 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 produced a relaxation of coronary vascular smooth muscle at drug levels which cause little or no negative inotropic effect.

12.2 Pharmacodynamics

Hemodynamics

Nicardipine produces significant decreases in systemic vascular resistance. In a study of intra-arterially administered nicardipine, the degree of vasodilation and the resulting decrease in blood pressure were more prominent in hypertensive patients than in normotensive volunteers. Administration of nicardipine to normotensive volunteers at dosages of 0.25 to 3 mg/hr for eight hours produced changes of less than 5 mmHg in systolic blood pressure and less than 3 mmHg in diastolic blood pressure.

An increase in heart rate is a normal response to vasodilation and decrease in blood pressure; in some patients these increases in heart rate may be pronounced. In placebo-controlled trials, the mean increases in heart rate were 7 ± 1 bpm in postoperative patients and 8 ± 1 bpm in patients with severe hypertension at the end of the maintenance period.

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 left ventricular end-diastolic pressure (LVEDP). There is evidence that nicardipine increases blood flow. Coronary dilatation induced by nicardipine improves perfusion and aerobic metabolism in areas with chronic ischemia, resulting in reduced lactate production and augmented oxygen consumption. In patients with coronary artery disease, nicardipine, administered after beta-blockade, significantly improved systolic and diastolic left ventricular function.

In congestive heart failure patients with impaired left ventricular function, nicardipine increased cardiac output both at rest and during exercise. Decreases in left ventricular end-diastolic pressure were also observed. However, in some patients with severe left ventricular dysfunction, it may have a negative inotropic effect and could lead to worsened failure.

"Coronary steal" has not been observed during treatment with nicardipine (Coronary steal is the detrimental redistribution of coronary blood flow in patients with coronary artery disease from underperfused areas toward better perfused areas.) Nicardipine has been shown to improve systolic shortening in both normal and hypokinetic segments of myocardial muscle. Radionuclide angiography has confirmed that wall motion remained improved during increased oxygen demand. (Occasional patients have developed increased angina upon receiving nicardipine capsules. Whether this represents coronary steal in these patients, or is the result of increased heart rate and decreased diastolic pressure, is not clear.)

