Package Insert

BENICARDINE

1. **Product Name**

   Benicardine

2. **Name and Strength of Active Ingredient (s)**

   Each mL contains: Nicardipine hydrochloride 1 mg

3. **Product Description**

   Clear, pale yellow sterile solution for injection

4. **Pharmacodynamics and Pharmacokinetics**

   Pharmacodynamics

   Nicardipine is a dihydropyridine calcium channel antagonist that inhibits the transmembrane influx of calcium ions into cardiac muscle and vascular smooth muscle without changing serum calcium ion concentrations. Vascular smooth muscles are more sensitive to this effect than cardiac muscles because depolarization of vascular smooth muscles is dependent on calcium ion influx whereas cardiac muscle depolarization involves both sodium and calcium ion influx.

   Nicardipine demonstrates strong coronary and cerebral vasodilatory activity. The selectivity for arterial and especially cardiac arterial vascular smooth muscle is reflected in relatively large and rapid changes in blood pressure (BP), with minimal inotropic cardiac effects and no significant venodilatory action.

   Intravenous (IV) nicardipine produces dose-related decreases in mean arterial BP (up to 30% reduction) and increases in heart rate (by up to 13% to 26%). The duration of these effects, which may be as long as 3 hours, have generally been greater in patients at rest than in those at exercise. Nicardipine-induced increases in heart rate are due to reflex adrenergic stimulation following reduction in total peripheral resistance.

   The degree of vasodilation and the resultant BP reduction were more prominent in hypertensive patients compared with normotensive volunteers given intra-arterial nicardipine. In normotensive volunteers, the administration of nicardipine 0.25 to 3 mg/hour for eight hours produced changes of <5 mmHg in systolic BP and <3 mmHg in diastolic BP.

   Nicardipine exerts a vasorelaxing action on cerebrovascular smooth muscles thereby enhancing blood flow and oxygenation into the brain. Thus, nicardipine may be beneficial in the prevention of cerebrovascular accidents among hypertensive patients.

   Hemodynamic studies in patients with coronary artery disease and normal or moderately abnormal left ventricular function have shown significant increases in cardiac output and coronary blood flow, with no significant change or a small decrease in left ventricular end-diastolic pressure (LVEDP). The ejection fraction is significantly increased by nicardipine.

Administration of nicardipine in patients with coronary artery disease results in increased coronary blood flow due to coronary vasodilatation and decreased coronary vascular resistance. The intracoronary administration of nicardipine in patients with coronary artery disease caused no direct myocardial depression. In patients receiving beta-blockers, the coadministration of nicardipine has further increased coronary blood flow and decreased coronary vascular resistance by as much as 21% and 32%, respectively.

Nicardipine's ability to decrease systemic vascular resistance (afterload) may improve blood distribution in ischemic myocardial tissue. Nicardipine-induced coronary dilation may improve perfusion and aerobic metabolism in chronically ischemic areas, leading to decreased lactate production and augmented oxygen consumption. The administration of nicardipine after beta-blockade in patients with coronary artery disease significantly improved systolic and diastolic ventricular function.

Nicardipine improves cardiac output both at rest and during exercise in patients with congestive heart failure. Decreases in LVEDP were also seen. However, nicardipine may have a negative inotropic effect in some patients with severe left ventricular dysfunction and could lead to worsened failure.

Coronary steal, the detrimental redistribution of coronary blood flow in patients with coronary artery disease from underperfused areas toward better perfused areas, has not been observed during nicardipine treatment. Nicardipine improves systolic shortening in both normal and hypokinetic segments of myocardial muscle. The wall motion remained improved during increased oxygen demand as confirmed by radionuclide angiography.

Pharmacokinetics

Nicardipine's pharmacokinetics is linear over the dosage range of 0.5 to 40 mg/hour. Rapid dose-related increases in nicardipine plasma concentrations are seen during the first two hours after the start of an infusion. Plasma concentrations increase at a much slower rate after the first few hours and approach steady state at 24 to 48 hours. On termination of the infusion, nicardipine plasma concentrations decrease rapidly, with at least 50% decrease during the first two hours post-infusion. Nicardipine's effects on blood pressure significantly correlate with plasma concentrations.

After IV infusion, nicardipine plasma concentrations decrease tri-exponentially, with a rapid early distribution phase (α-half-life of 3 minutes), an intermediate phase (β-half-life of 45 minutes), and a slow terminal phase (γ-half-life of 14 hours) that can only be detected after long-term infusions. Nicardipine's total plasma clearance is 0.4 L/hr.-kg. The apparent volume of distribution is 8.3 L/kg.

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

Nicardipine has been shown to be rapidly and extensively metabolized by the liver and its excretion is mainly renal. It does not induce or inhibit its own metabolism and does not induce or inhibit hepatic microsomal enzymes.

After concomitant administration of a radioactive intravenous dose of nicardipine with an oral 30 mg dose given every 8 hours, 49 and 43% of the radioactivity was recovered in urine and feces, respectively, within 96 hours. None of the dose was recovered as unchanged nicardipine.

5. Indication

- Moderate to severe hypertension where immediate correction of blood pressure (BP) is required (e.g., hypertensive emergency or urgencies).
- Peri-operative and post-operative hypertension.
- Short-term treatment of essential hypertension when oral therapy is not feasible or desirable.

6. Recommended Dose

Nicardipine injection is intended for intravenous infusion. Dosage must be individualized depending on the severity of hypertension and patient response during dosing.

Monitor BP and heart rate both during and after the infusion; avoid too rapid or excessive reduction in either systolic or diastolic BP during parenteral treatment.

Preparation of Infusion Solution:

Dilution Instructions: Nicardipine Injection must be diluted prior to administration. It is administered by slow continuous IV infusion at a concentration of 0.1-0.2 mg/mL. Nicardipine infusion solution is prepared by adding the necessary volume of nicardipine injection to a compatible infusion fluid. (see Table 1)

Table 1. Nicardipine Injection Dilution Table

Format	Amount (Volume) of Nicardipine Injection	Volume of IV Infusion Solution Needed (Diluent)*	Total Volume of Infusion Solution (mL Drug + mL Diluent)	Desired Final Concentration of Infusion Solution
2 mg per 2 mL	10 mg (10 mL) or 5 vials	90 mL	100 mL	0.1 mg/mL
	25 mg (25 mL) or 12½ vials	225 mL	250 mL	0.1 mg/mL
10 mg per 10 mL	10 mg (10 mL) or 1 vial	90 mL	100 mL	0.1 mg/mL
	25 mg (25 mL) or 2½ vials	225 mL	250 mL	0.1 mg/mL
25 mg per 25 mL	25 mg (25 mL) or 1 vial	225 mL	250 mL	0.1 mg/mL

*** Notes:**

- Nicardipine injection has been found to be compatible and stable in glass or polyvinyl chloride or polyethylene or polypropylene containers with the following infusion fluids:
  - Dextrose (5%) Injection
  - Dextrose (5%) and Sodium Chloride (0.45%) Injection
  - Dextrose (5%) and Sodium Chloride (0.9%) Injection

- Dextrose (5%) with 40 mEq Potassium
- Sodium Chloride (0.45%) Injection
- Sodium Chloride (0.9%) Injection

- Nicardipine Injection **is NOT** compatible with Sodium Bicarbonate (5%) Injection or Lactated Ringer's Injection.
- The diluted solution is stable for 24 hours at room temperature in glass or PVC or polyethylene or polypropylene containers.

Dosage as a Substitute for Oral Nicardipine:

For patients who are maintained on oral nicardipine therapy and are being switched to IV therapy, the infusion rates necessary to produce an average plasma concentration equivalent to steady state oral doses are as follows (see Table 2):

Table 2. Equivalent Oral and IV Nicardipine Doses

Oral Dose	***Equivalent IV Infusion Rate***
20 mg every 8 hours	0.5 mg/hour
30 mg every 8 hours	1.2 mg/hour
40 mg every 8 hours	2.2 mg/hour

7. Mode of Administration

<u>Dosage for Initiation of Therapy in Patients not Currently Receiving Antihypertensive Therapy</u>:

Administer nicardipine injection by slow continuous IV infusion at a concentration of 0.1-0.2 mg/mL. With constant infusion in patients not currently receiving antihypertensive therapy, BP begins to decrease within minutes. BP reaches approximately 50% of its ultimate reduction in about 45 minutes and does not reach final steady state for about 50 hours. (see Table 3)

Table 3. Nicardipine IV Infusion Dosing and Titration

Indication/Effect	**Initial Infusion Rate**	**Dose Titration**	**Maximum Dose**
For gradual BP reduction	50 mL/hour (5 mg/hour)	Increase infusion rate by 25 mL/hour (2.5 mg/hour) **every 15 minutes** if optimal BP is not achieved at initial dose.	150 mL/hour (15 mg/hour)
For more rapid BP reduction	50 mL/hour (5 mg/hour)	Increase infusion rate by 25 mL/hour (2.5 mg/hour) **every 5 minutes** if optimal BP is not achieved at initial dose.	150 mL/hour (15 mg/hour)
Maintenance Dose: Adjust infusion rate as needed to maintain desired response. Following achievement of BP goal, decrease infusion rate to 30 mL/hour (3 mg/hour)			
Or, as prescribed by a physician.			

Conditions Requiring Infusion Adjustment:

Hypotension or Tachycardia: Discontinue infusion in case of hypotension or tachycardia. When BP and heart rate have stabilized, restart nicardipine IV infusion at low doses (e.g., 30 to 50 mL/hour) and adjust to maintain desired BP.

Infusion Site Changes: It is recommended that the infusion site be changed every 12 hours to minimize the risk of peripheral venous irritation.

Impaired Cardiac, Liver or Renal Function: Patients with congestive heart failure or impaired liver or renal function should be closely monitored when titrating nicardipine IV.

Transfer to Oral Antihypertensives

When transferring treatment to an oral antihypertensive other than nicardipine oral capsule or tablet, therapy should be started upon discontinuation of nicardipine IV.

If nicardipine tablets or capsules are to be used, the first dose of a thrice daily oral regimen should be taken 1 hour prior to discontinuation of nicardipine IV infusion.

8. Contraindication

- Known hypersensitivity to nicardipine
- Advanced aortic stenosis

9. Warning and Precaution

Excessive Pharmacologic Effects

Carefully monitor patient's BP and heart rate since nicardipine decreases peripheral vascular resistance and occasionally causes excessive and poorly tolerated hypotension or tachycardia.

Use with caution in patients with acute cerebral infarction or hemorrhage, and systemic hypotension should be avoided in these patients.

Rapid Decreases in BP

Although nicardipine IV has not been associated with adverse effects secondary to an excessively rapid decrease in BP, reduction of BP should be accomplished over as long a time period as is compatible with patient's clinical status.

Use in Patients with Angina

Increases in frequency, duration, or severity of angina have been observed in chronic oral nicardipine therapy. There have been reports of induction or exacerbation of angina in less than 1% of patients with coronary artery disease given nicardipine.

Use in Patients with Congestive Heart Failure

Use with caution in patients with congestive heart failure, especially in those receiving concomitant beta-adrenergic blocking agents, since nicardipine has been shown in some *in vitro* and clinical studies to have negative inotropic effect and may precipitate or worsen heart failure. If concomitant beta-blocker is intended to be withdrawn, beta-blocker withdrawal should be done by gradual dose reduction, preferably over 8 to 10 days.

Use in Patients with Impaired Liver Function

Use with caution in patients with impaired liver function or reduced hepatic blood flow since nicardipine is extensively metabolized in the liver. Nicardipine bioavailability and elimination half-life are increased substantially in patients with severe hepatic impairment.

Use in patients with Impaired Renal Function

Nicardipine IV should be used with caution and dosage titrated carefully in patients with impaired renal function.

Use in Patients with Pheochromocytoma

Administer with caution in patients with pheochromocytoma since there is limited clinical experience on the use of nicardipine IV in hypertension associated with pheochromocytoma.

Central Vein Infusion Site

Nicardipine IV should be administered through central veins rather than arteries or small peripheral veins (e.g., those on the dorsum of the hand or wrist) to decrease the possibility of venous thrombosis, phlebitis, local irritation, swelling extravasation, and rarely, vascular impairment.

10. Interactions with Other Medicaments

Beta-blockers (e.g., propranolol): Beta-blockers result in an excessive decrease in BP and a reduction in cardiac function in patients with congestive heart failure. Reduce dosage or discontinue use of either drug when necessary.

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

Digoxin: Nicardipine may increase plasma levels of digitalis preparations. Evaluate digoxin levels when concomitant therapy with nicardipine IV is initiated.

Fentanyl Anesthesia: Concomitant use of fentanyl anesthesia with a calcium channel blocker has been reported to cause hypotension. Although such interactions were not seen in studies with nicardipine IV, an increased volume of circulating fluids might be necessary in the occurrence of such interactions.

Ciclosporin: Concomitant administration increases ciclosporin plasma levels. Ciclosporin dosage should therefore be reduced accordingly in patients treated with nicardipine.

Other antihypertensive agents: Monitor patients to identify and treat promptly any undesirable effects from concomitant administration.

In vitro Interaction: No changes in plasma protein binding of nicardipine were observed when furosemide, propranolol, dipyridamole, warfarin, quinidine, or naproxen were added to human plasma *in vitro*.

11. Pregnancy and Lactation

Pregnancy

Pregnancy Category C. There are no adequate and controlled studies to date using nicardipine in pregnant women. Nicardipine should be used in pregnancy only when the potential benefits justify the potential risks to the fetus.

There was an increased embryolethality observed when nicardipine was administered orally to pregnant rabbits at a dose equivalent to a human oral dose of about 48 mg/kg/day (24 times the maximum recommended human oral dose and one associated with marked maternal body weight gain suppression). There were no adverse effects on the fetus, though there was increased maternal mortality, when nicardipine was given 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 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 maximum recommended human oral dose); however, dystocia, reduced birth weight, neonatal survival and neonatal weight gain were reported.

Lactation

Nicardipine is distributed into milk in high concentrations in rats. Because of potential for serious adverse reactions to nicardipine in breastfeeding infants, it is recommended that women who breastfeed not be given the drug.

Use in Children

The safety and effectiveness of nicardipine in patients below 18 years old have not been established.

Use in Elderly

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

12. Undesirable Effects

Adverse effects that have been reported with nicardipine IV are as follows:

Body as a Whole: Asthenia, chest pain, fever, neck pain, malaise, fatigue, peripheral or facial edema, infection, arthralgia

Cardiovascular: Hypotension, postural hypotension, exertional hypotension, tachycardia, ECG abnormality, ventricular extrasystoles, extrasystoles, hemopericardium, hypertension, supraventricular tachycardia, syncope, vasodilation, ventricular tachycardia, angina pectoris, atrioventricular block, ST segment depression, inverted T wave, deep-vein thrombophlebitis, sick sinus syndrome, flushing, palpitations, myocardial infarction, atrial fibrillation, pericarditis, peripheral vascular disorder

Digestive: Abdominal pain, nausea, vomiting, dyspepsia, constipation, diarrhea, dry mouth, anorexia, heartburn

Metabolic and Nutritional: Hypokalemia, hypophosphatemia, hyperglycemia, abnormal hepatic function test results, increased plasma renin concentration

Nervous: Headache, dizziness, hypesthesia, intracranial hemorrhage, paresthesia, confusion, hypertonia, somnolence, insomnia, hot flashes, vertigo, hyperkinesia, impotence, mental depression, anxiety, cerebrovascular accident, cerebral ischemia, lassitude, nervousness, lightheadedness

Hemic and Lymphatic: Thrombocytopenia

Respiratory: Dyspnea, respiratory disorder, rhinitis, sinusitis

Skin and Appendages: Sweating, injection site reaction and pain, rash

Urogenital: Polyuria, hematuria, increased urinary frequency, nocturia, urinary retention

Special Senses: Conjunctivitis, abnormal or blurred vision, ear disorder, tinnitus

13. Overdose and Treatment

Studies in laboratory animals showed that lethal nicardipine overdose may cause systemic hypotension, bradycardia (following initial tachycardia) and progressive atrioventricular conduction block. Reversible hepatic function abnormalities and sporadic focal hepatic necrosis were also noted in test animals.

Standard measures including monitoring of cardiac and respiratory functions should be implemented as part of the management of nicardipine overdosage. Place the patient in supine position with legs elevated to avoid cerebral anoxia. If this is not adequate, increase plasma volume by infusion of glucose, saline or dextran. Frequent BP monitoring is essential. In case of accompanying bradycardia, administer atropine IV. Pressor therapy and intravenous calcium gluconate should be reserved for patients with hypotension unresponsive to IV fluids.

14. Storage Condition

Store below 30°C. Protect from light.

15. Dosage Forms and Packing Available

2, 10, 25 mL amber glass vial (Type I) with aluminium flip-off/Chlorobutyl packed or unpacked in paper box of 1, 5, 10, 20, 25, 50 and 100 vials.

16. Name and Address of Manufacturer/ Marketing Authorization Holder

ABLE MEDICAL COMPANY LIMITED

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Mahasarakham 44160, Thailand

17. Date of revision of package insert

6 June 2023