

# NICARDIPINE

## NICABLOC

1 mg/mL Solution for IV Infusion  
CALCIUM CHANNEL BLOCKER



### FORMULATION:

Each mL contains:  
Nicardipine hydrochloride ..... 1 mg

### PRODUCT DESCRIPTION:

A clear, pale yellowish-green liquid.

### PHARMACODYNAMICS/PHARMACOKINETICS:

**Pharmacodynamics**  
Nicardipine is a second generation slow calcium channel inhibitor, and belongs to the phenyl-dihydropyridine group. Nicardipine has a greater selectivity for L-type calcium channels in vascular smooth muscle than cardiac myocytes. At very low concentrations it inhibits the influx of calcium into the cell. Its action is produced mainly on arterial smooth muscle. This is reflected in relatively large and rapid changes in blood pressure, with minimal inotropic changes in cardiac function (baroreflex effect). Administered by systemic route, nicardipine is a potent vasodilator which diminishes total peripheral resistance and lowers blood pressure. Heart rate is temporarily increased; as a result of a decrease in after-load, cardiac output is markedly and durably increased. In humans, the vasodilator action also occurs in both acute dose administration and chronic administration in the large and small arteries, increasing blood flow and improving arterial compliance. Renal vascular resistance is decreased.

### Pharmacokinetics

**Distribution**  
Nicardipine is highly protein bound in human plasma over a wide concentration range.

### Metabolism

Nicardipine is metabolized by cytochrome P450 3A4. Studies involving either a single dose, or administration 3 times daily for 3 days, have shown that less than 0.03% of unchanged nicardipine is recovered in the urine in humans after oral or intravenous administration. The most abundant metabolite in human urine is the glucuronide of the hydroxy form, which is formed by the oxidative cleaving of the N-methylbenzyl moiety and the oxidation of the pyridine ring.

**Excretion**  
After co-administration of a radioactive intravenous dose of nicardipine with an oral 30 mg dose given every 8 hours, 49% of the radioactivity was recovered in the urine and 43% in the feces within 96 hours. None of the dose was recovered as unchanged nicardipine in the urine. The elimination profile of the drug following an intravenous dose consists of three phases, with corresponding half-life: alpha 6.4 min, beta 1.5 hours, gamma 7.9 hours.

**Renal impairment**  
The pharmacokinetics of intravenously administered nicardipine was studied in subjects with severe renal dysfunction requiring hemodialysis (creatinine clearance < 10 mL/min), mild/moderate renal dysfunction (creatinine clearance 10 - 50 mL/min) and normal renal function (creatinine clearance >50 mL/min). At steady state, C<sub>max</sub> and AUC were significantly higher and clearance significantly lower in subjects with mild/moderate renal function compared with in subjects with normal renal function. There were no significant differences in the principal pharmacokinetic parameters between severe renal dysfunction and normal renal dysfunction.

### INDICATIONS:

- Used for the treatment of acute life-threatening hypertension, particularly in the event of:
- Malignant arterial hypertension/Hypertensive encephalopathy
  - Aortic dissection, when short acting beta-blocker therapy is not suitable, or in combination with a beta-blocker when beta-blockade alone is not effective
  - Severe pre-eclampsia, when other intravenous antihypertensive agents are not recommended or are contraindicated
  - Nicardipine is also indicated for the treatment of post-operative hypertension

### DOSEAGE AND ADMINISTRATION:

Nicardipine should only be administered by specialists in well controlled environments, such as hospitals and intensive care units, with continuous monitoring of blood pressure. The speed of administration must be accurately controlled by the use of an electronic syringe driver or a volumetric pump. Blood pressure and heart rate must be monitored at least every 5 minutes during the infusion, and then until vital signs are stable, but at least for 12 hours after the end of the administration of nicardipine.

The antihypertensive effect will depend on the administered dose. The dosage regimen to achieve the desired blood pressure can vary depending on the targeted blood pressure, the response of the patient, and the age or status of the patient. Unless given by a central venous line, dilute to a concentration of 0.1 - 0.2 mg/mL before use.

**Adults**  
**Initial dose:** Treatment should start with the continuous administration of nicardipine at a rate of 3-5 mg/h for 15 minutes. Rates can be increased by increments of 0.5 or 1 mg every 15 minutes. The infusion rate should not exceed 15 mg/h.

**Maintenance dose:** When the target pressure is reached, the dose should be reduced progressively, usually to between 2 and 4 mg/h, to maintain the therapeutic efficacy.

**Transition to an oral antihypertensive agent:** discontinue nicardipine or titrate downward while appropriate oral therapy is established. When an oral antihypertensive agent is being instituted, consider the lag time of onset of the oral agent's effect. Continue blood pressure monitoring until desired effect is achieved.

A switch can also be made to oral nicardipine 20mg capsules at dosage of 60 mg/day in 3 daily doses, or to nicardipine 50 mg extended-release tablets, at dosage of 100 mg/day, in 2 daily doses.

### Elderly

Clinical studies of nicardipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Elderly patients may be more sensitive to nicardipine effects because of impaired renal and/or hepatic function. It is recommended to provide a continuous infusion of nicardipine starting at the dose of 1 to 5 mg/h, depending on the blood pressure and clinical situation. After 30 minutes, depending on the effect observed, the rate should be increased or decreased by increments of 0.5 mg/h. The rate should not exceed 15 mg/h.

### Pediatric population

The safety and efficacy in low birth weight infants, newborns, nursing infants, infants, and children has not been established. Nicardipine should only be used for life-threatening hypertension in pediatric intensive care settings or post-operative contexts.

**Initial dose:** In case of emergency, a starting dose of 0.5 to 5 mcg/kg/min is recommended.

**Maintenance dose:** The maintenance dosage of 1 to 4 mcg/kg/min is recommended. Nicardipine should be used with particular caution in children with renal impairment. In this case, only the lowest dosage should be used.

### Pregnancy

It is recommended to provide a continuous infusion of nicardipine starting at 1 to 5 mg/h, depending on the blood pressure and clinical situation. After 30 minutes, depending on the effect observed, this rate can be increased or decreased by increments of 0.5 mg/h.

Doses higher than 4mg/h are generally not exceeded in the treatment of pre-eclampsia, however the rate should not exceed 15 mg/h.

### Hepatic Impairment

Nicardipine should be used with particular caution in these patients. Since nicardipine is metabolized in the liver, it is recommended to use the same dose regimens as for elderly patients in patients with impaired liver function or reduced hepatic blood flow.

### Renal Impairment

Nicardipine should be used with particular caution in these patients. In some patients with moderate renal impairment, a significantly lower systemic clearance and higher area under the curve (AUC) have been observed. Therefore, it is recommended to use the same dose regimens as for elderly patients in patients with renal impairment.

### Method of administration

Nicardipine should be administered by continuous intravenous infusion only.

### CONTRAINDICATIONS:

- Known hypersensitivity to nicardipine or to any of the excipients.  
Severe aortic stenosis  
Compensatory hypertension, i.e. in case of an arteriovenous shunt or aortic coarctation  
Unstable angina  
Within 8 days after myocardial infarction  
Patients with rare hereditary problems of fructose intolerance should not take this medicine

### WARNINGS AND PRECAUTIONS:

#### Warnings

Rapid pharmacologic reductions in blood pressure may produce systemic hypotension and reflex tachycardia. If either occurs with nicardipine, consider decreasing the dose by half or stopping the infusion.  
Bolu administration or intravenous administration not controlled by the use of an electronic syringe driver or a volumetric pump is not recommended and can increase the risk of serious hypotension, particularly in the elderly, in children, in patients with renal or hepatic impairment and in pregnancy.

#### Cardiac failure

Nicardipine should be used with caution in patients with congestive heart failure or pulmonary edema, particularly when these patients are receiving concomitant beta blockers, as worsening of cardiac insufficiency may occur.

Ischaemic cardiovascular disease.  
Nicardipine is contraindicated in unstable angina and immediately following myocardial infarction.

Nicardipine should be used with caution in patients with suspected coronary ischaemia. Occasionally, patients have developed an increased frequency, duration, or severity of angina upon starting or increasing nicardipine dosage, or during the course of treatment.

#### Pregnancy

Due to the risk of severe maternal hypotension and potentially fatal foetal hypoxia, the decrease in blood pressure should be progressive and always closely monitored. Due to the possible risk of pulmonary edema or excessive decrease in blood pressure, caution should be taken if magnesium sulphate is used concomitantly.

**Patients with history of hepatic dysfunction or impaired hepatic function**  
Rare cases of abnormal hepatic function possibly associated with the use of nicardipine have been reported. Potential risk groups are patients with a history of hepatic dysfunction or those with impaired hepatic function at the initiation of treatment with nicardipine.

**Patients with portal hypertension**  
Intravenous nicardipine at high doses has been reported to worsen portal vein hypertension and portal-systemic collateral blood flow index in cirrhotic patients.

**Patients with pre-existing elevated intracranial pressure**  
Intracranial pressure should be monitored, to allow calculation of the cerebral perfusion pressure.

#### Patients with Stroke

Nicardipine should be used with caution in patients with acute cerebral infarction. A hypertensive episode which often accompanies a stroke is not an indication for emergency antihypertensive therapy. The use of antihypertensive drugs is not recommended in ischemic stroke patients unless acute hypertension precludes the administration of an adequate treatment (e.g. thrombolysis) or there is other end organ damage which is life-threatening in the short term.

### Precautions

**Combination with beta-blockers**  
Caution should be exercised when using nicardipine in combination with a beta blocker in patients with decreased cardiac function. In such case, the dosology of the beta blocker should be individualized to the clinical situation.

### Injection site reactions

Infusion site reactions can occur, particularly with prolonged duration of administration and in peripheral veins. It is advised to change the infusion site in case of any suspicion of infusion site irritation. The use of a central venous line or of a greater dilution of the solution could reduce the risk of occurrence of infusion site reaction.

### Pediatric population

The safety and efficacy of nicardipine IV has not been tested in controlled clinical trials in infants or children, thus special care is required in this population.

### Excipient warnings:

This product contains sorbitol. Patients with rare hereditary problem of fructose intolerance should not take this medicine.

### PREGNANCY AND LACTATION:

#### Pregnancy

Limited pharmacokinetic data have shown that nicardipine I.V. does not accumulate and has a low placental transfer.

In clinical practice, the use of nicardipine during the first two trimesters in a limited number of pregnancies has not revealed any malformative or particular fetotoxic effect to date.

The use of nicardipine for severe pre-eclampsia during the third trimester of pregnancy could potentially produce an undesirable tocolytic effect which could potentially interfere with the spontaneous induction of labour.

Acute pulmonary edema has been observed when nicardipine has been used as tocolytic during pregnancy, especially in cases of multiple pregnancy (twins or more), with the intravenous route and/or concomitant use of beta-2 agonists. Nicardipine should not be used in multiple pregnancies or in pregnant women with compromised cardiovascular condition, except if there is no other acceptable alternative.

#### Lactation

Nicardipine and its metabolites are excreted in human milk at very low concentrations. There is insufficient information on the effects of nicardipine in newborns/infants. Nicardipine should not be used during breast-feeding.

### INTERACTIONS:

Enhancement of negative inotropic effect.  
Nicardipine may enhance the negative inotropic effect of beta-blockers and may cause heart failure in patient with latent or uncontrolled heart failure

#### Dantrolene

In animal studies, administration of verapamil and intravenous dantrolene has caused fatal ventricular fibrillation. The combination of a calcium channel inhibitor and dantrolene is therefore potentially dangerous.

#### Magnesium

Due to the possible risk of pulmonary edema or excessive decrease in blood pressure, caution should be taken if magnesium sulphate is used concomitantly.

#### CYP3A4 inducers and inhibitors

Nicardipine is metabolized by cytochrome P450 3A4. Co-administration of CYP 3A4 enzyme-inducing agents (e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone and rifampicin) may cause a decrease in the plasma concentrations of nicardipine.

Co-administration of CYP3A4 enzyme-inhibiting agents (e.g. cimetidine, itraconazole and grapefruit juice) may cause an increase in the plasma concentrations of nicardipine. Co-administration of calcium channel blockers with itraconazole has shown an increased risk of adverse events, in particular edema due to a decreased metabolism of the calcium channel blocker in the liver.

#### Cyclosporine, tacrolimus and sirolimus

Concomitant administration of nicardipine and cyclosporine, tacrolimus or sirolimus results in elevated plasma cyclosporine/tacrolimus levels. Blood levels should be monitored and dosage of immunosuppressant and/or nicardipine should be reduced, if required.

#### Digoxin

Nicardipine has been reported to increase the plasma levels of digoxin in pharmacokinetic studies. Digoxin levels should be monitored when concomitant therapy with nicardipine is initiated.

#### Potential additive antihypertensive effect

Concomitant medications which could potentiate the antihypertensive effect of nicardipine include baclofen, alpha-blockers, tricyclic antidepressants, neuroleptics, opioids and amifostine

#### Decrease of antihypertensive effect

Nicardipine in combination with intravenous corticosteroids and tetracosactide (except for hydrocortisone used as replacement therapy in Addison's disease) may cause a decrease in the antihypertensive effect

#### Inhalational anaesthetics

The co-administration of nicardipine with inhalational anaesthetics could induce a potential additive or synergistic hypotensive effect, as well as an inhibition by anaesthetics of the baroreflex heart rate increase associated with peripheral vasodilators. Limited clinical data suggests that the effects of inhaled anaesthetics (e.g. isoflurane, sevoflurane and enflurane) on nicardipine appear to be moderate.

#### Competitive neuromuscular blockers

Limited data suggest that nicardipine, as other calcium channel blockers, enhances neuromuscular block possibly by acting at the post-junctional region. Vecuronium infusion dose requirements could be reduced by the concurrent use of nicardipine. Reversal of neuromuscular block by neostigmine appears not to be affected by nicardipine infusion. No additional monitoring is required.

### ADVERSE DRUG REACTIONS:

The majority of undesirable effects are the consequence of the vasodilator effects of nicardipine. The most frequent events are headache, dizziness, peripheral edema, palpitations and flushing

Frequency categories are defined according to the following convention: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) and not known (cannot be estimated from the available data).

System organ class	Frequency
Blood and lymphatic system disorders	Not known - thrombocytopenia
Immune system disorder	Not known - anaphylactic reaction
Nervous system disorders	Very common - headache Common - dizziness
Cardiac disorders	Common - lower limb edema, palpitations Common - hypotension, tachycardia Not known - atrioventricular block, angina pectoris
Vascular disorders	Common - orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Not known - pulmonary edema
Gastrointestinal disorders	Common - nausea, vomiting Not known - paralytic ileus
Skin and subcutaneous tissue disorders	Common - flushing Not known - erythema
General disorders and administration site conditions	Not known - phlebitis
Investigations	Not known - hepatic enzyme increased

\*cases have been also reported when used as tocolytic during pregnancy

### OVERDOSE AND TREATMENT:

#### Symptoms

Overdose with nicardipine hydrochloride can potentially result in marked hypotension, bradycardia, palpitations, flushing, drowsiness, collapse, peripheral edema, confusion, slurred speech and hyperglycaemia. In laboratory animals, overdose also resulted in reversible hepatic function abnormalities, sporadic focal hepatic necrosis and progressive atrioventricular conduction block.

#### Treatment

In case of an overdose it is recommended to use routine measures including monitoring of cardiac and respiratory function. In addition to general supportive measures, intravenous calcium preparations and vasopressors are clinically indicated for patients exhibiting the effects of calcium entry blockade. Major hypotension can be treated by intravenous infusion of any plasma volume expander and supine position with the legs elevated. Nicardipine is not dialyzable.

### STORAGE CONDITION:

Store at temperatures not exceeding 30°C

### DOSEAGE FORMS AND PACKAGING AVAILABLE:

**Dosage form:** Solution for IV infusion  
**Packaging available:** USP Type I amber coloured glass ampoule x 10 mL (Box of 5's in PVC plastic tray)

### CAUTION:

Food, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

### ADR REPORTING STATEMENT:

For suspected adverse drug reaction, report to the FDA: [www.fda.gov/ahr](http://www.fda.gov/ahr)  
Seek medical attention immediately at the first sign of any adverse drug reaction

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