

Date: 22 April 2021

Swissmedic, Swiss Agency for Therapeutic Products

## ***Swiss Public Assessment Report***

### **Nicardipin Labatec**

**International non-proprietary name:** nicardipine hydrochloride

**Pharmaceutical form:** solution for infusion

**Dosage strength:** 10 mg/10 mL

**Route(s) of administration:** intravenous use

**Marketing Authorisation Holder:** Labatec Pharma SA

**Marketing Authorisation No.:** 67680

**Decision and Decision date:** approved on 22 March 2021

**Note:**

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

**About Swissmedic**

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

**About the Swiss Public Assessment Report (SwissPAR)**

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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## 1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
C <sub>max</sub>	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

## 2 Background Information on the Procedure

### 2.1 Applicant's Request(s)

#### New Active Substance status

The applicant requested the status of a new active entity for the active substance nicardipine hydrochloride of the medicinal product mentioned above.

#### Authorisation in accordance with Art. 14 para. 1 a<sup>bis-quater</sup> TPA

The applicant requested a simplified authorisation in accordance with Art. 14 para. 1 a<sup>bis-quater</sup> TPA.

### 2.2 Indication and Dosage

#### 2.2.1 Requested Indication

Nicardipine 10 mg/10 ml solution for injection is indicated 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 contra-indicated

Nicardipine is also indicated for the treatment of post-operative hypertension

#### 2.2.2 Approved Indication

Intravenous nicardipine is indicated 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 contra-indicated.

Nicardipine is also indicated for the treatment of post-operative hypertension.

#### 2.2.3 Requested Dosage

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.

### Special dosing instructions

#### Patients with 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.

#### Patients with 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.

#### Elderly patients

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.

#### Children and adolescents

The safety and efficacy in low birth weight infants, newborns, nursing infants, infants, and children have not been established. Nicardipine should only be used for life-threatening hypertension in paediatric 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 dose 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 4 mg/h are generally not exceeded in the treatment of pre-eclampsia, however the rate should not exceed 15 mg/h. (See "Special warnings and precautions for use", "Fertility, pregnancy and lactation" "Undesirable effects")

#### Method of administration

Nicardipine should be administered by continuous intravenous infusion only.

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.

### 2.2.4 Approved Dosage

(see appendix)

**2.3 Regulatory History (Milestones)**

Application	19 August 2019
Formal control completed	14 October 2019
List of Questions (LoQ)	31 January 2020
Answers to LoQ	28 July 2020
Predecision	22 October 2020
Answers to Predecision	22 December 2020
Final Decision	22 March 2021
Decision	approval

### 3 Quality Aspects

#### 3.1 Drug Substance

##### Drug Substance

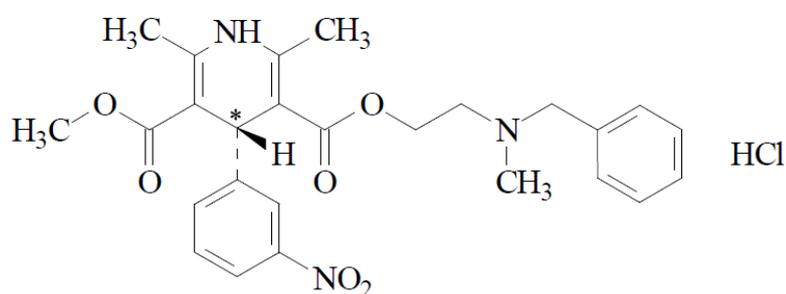
INN: Nicardipine Hydrochloride

Chemical name: 2-[Benzyl(methyl)amino]ethyl methyl (4RS)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate hydrochloride

Molecular formula:  $C_{26}H_{29}N_3O_6 \cdot HCl$

Molecular mass: 516.0 g/mol

Molecular structure:



And enantiomer

Appearance: Pale yellow or pale greenish-yellow, crystalline powder

Solubility: Slightly soluble in water, soluble in methanol, sparingly soluble in ethanol 96%.

Nicardipine is the subject of an active substance master file (ASMF).

Synthesis of the active substance from the designated starting materials has been adequately described. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis. No materials of animal or human origin are used in the production of the active substance.

Appropriate proof-of-structure data have been supplied for the active substance. All potential impurities have been identified and monitored appropriately.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data have been provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been provided supporting a suitable retest period when stored in the proposed packaging.

### **3.2 Drug Product**

The drug product is a sterile clear solution.

The composition is adequately described, qualitatively and quantitatively.

Suitable pharmaceutical development data have been provided for the finished product formulation and manufacturing process, including establishment of the Quality Target Product Profile (QTPP), the Critical Quality Attributes (CQA) and the Critical Process Parameters (CPP).

A satisfactory batch formula has been provided for the manufacture of the product, together with an appropriate account of the manufacturing process, which is described in sufficient detail. The manufacturing process has been validated on three commercial-scale batches. The results are satisfactory.

The finished product specification is satisfactory. The test methods have been described and validated adequately. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

The finished product is packed in type I brown one point cut (OPC) ampoules.

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf life of 2 years for the ampoules is set, with storage recommendation “Do not store above 25°C” and protected from light. This is satisfactory.

### **3.3 Quality Conclusions**

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

#### **4 Nonclinical Aspects**

Swissmedic has not assessed the primary data relating to preclinical aspects of this application and is taking over the results of the assessment of the foreign reference authority of France. The current SwissPAR relating to preclinical aspects refers to the publicly available Assessment Report for Nicardipin Aguetant 10 mg /10 ml issued by the French authority.

## **5 Clinical and Clinical Pharmacology Aspects**

Swissmedic has not assessed the primary data relating to clinical aspects of this application and is taking over the results of the assessment of the foreign reference authority of France. The current SwissPAR relating to clinical aspects refers to the publicly available Assessment Report for Nicardipin Aguetant 10 mg /10 ml issued by the French authority

### **5.1 Approved Indication and Dosage**

See information for healthcare professionals in the Appendix.

## **6 Risk Management Plan Summary**

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.

The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

## 7 Appendix

### 7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Nicardipin Labatec was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see [www.swissmedicinfo.ch](http://www.swissmedicinfo.ch)).

**Note:**

The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

### **Nicardipin Labatec 10 mg / 10 ml, solution for injection**

*The efficacy and safety of Nicardipin Labatec 10 mg / 10 ml have only been summarily checked by Swissmedic. The authorization of Nicardipin Labatec 10 mg / 10 ml is based on that of Nicardipin Aguettant 10 mg / 10 ml, which contains the same active ingredient and is authorized in France with the last product information updated in January 2019.*

#### **Composition**

##### *Active substances*

Nicardipini hydrochloridum.

##### *Excipients*

Sorbitolum 50mg/ml (E 420), Natrii citras dihydricus, Acidum citricum monohydricum, Acidum hydrochloridum and/aut Natrii hydroxidum ad pH, Aqua ad iniectionabile.

#### **Pharmaceutical form and active substance quantity per unit**

Solution for injection.

1 ampoule of 10 ml contains: 10 mg of Nicardipini hydrochloridum (1 mg /ml).

#### **Indications/Uses**

Intravenous nicardipine is indicated 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 contra-indicated.

Nicardipine is also indicated for the treatment of post-operative hypertension.

#### **Dosage/Administration**

The antihypertensive effect depends on the administered dose. The dosage to achieve the desired blood pressure can vary depending on the targeted blood pressure, the response of the patient, and the age or general 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 before onset of the oral agent's effect. Continue blood pressure monitoring until desired effect is achieved.

### **Special dosage instructions**

#### *Patients with hepatic disorders*

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

#### *Patients with renal disorders*

Nicardipine should be used with particular caution in these patients. In some patients with moderate renal failure, 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 failure.

#### *Elderly patients*

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 the effects of nicardipine because of impaired renal and/or hepatic function. It is recommended to provide a continuous infusion of nicardipine starting at a 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 can be increased or decreased by increments of 0.5 mg/h. The rate should not exceed 15 mg/h.

#### *Children and adolescents*

The safety and efficacy of nicardipine 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 paediatric 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 dose of 1 to 4 mcg/kg/min is recommended.

Nicardipine should be used with caution in children with renal failure. 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, the rate can be increased or decreased by increments of 0.5 mg/h.

Doses higher than 4 mg /h are generally not exceeded in the treatment of pre-eclampsia. However, the rate should not exceed 15 mg/h (see “Warnings and precautions”, “Pregnancy, lactation”, “Undesirable effects”).

### ***Mode of administration***

Nicardipine should only be administered by continuous intravenous infusion.

Nicardipine should only be administered by specialists in a well-controlled medical environment, such as hospitals and intensive care units, with continuous monitoring of blood pressure. The rate of administration should be precisely controlled using an electronic syringe driver or a volumetric pump. The blood pressure and heart rate should be monitored at a minimum of every 5 minutes during infusion, then until stabilisation of vital signs and at least 12 hours after the end of nicardipine administration.

### **Contraindications**

- Hypersensitivity to the active substance or to any of the excipients,
- Severe aortic stenosis,
- Compensatory hypertension, in case of an arteriovenous shunt or aortic coarctation,
- Unstable angina,
- Within 8 days after myocardial infarction.

### **Warnings and precautions**

It is recommended to administer nicardipine with caution to avoid an excessive fall in blood pressure. In fact, 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.

Bolus 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 failure and in pregnancy.

#### ***Cardiac failure***

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

#### ***Ischaemic cardiovascular disease***

Nicardipine is contra-indicated in unstable angina and immediately following myocardial infarction (see “Contraindications”).

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 oedema or excessive decrease in blood pressure, caution should be taken if magnesium sulphate is used concomitantly.

As cases of acute pulmonary oedema have been reported during pregnancy, nicardipine should be administered with caution in pregnant women, who should be closely monitored to detect possible onset of an acute pulmonary oedema. If an acute pulmonary oedema occurs, nicardipine treatment should be immediately stopped and an appropriate treatment should be initiated.

### *Patients with history of hepatic dysfunction or hepatic failure*

Rare cases of abnormal hepatic function possibly associated with the administration of nicardipine have been reported. Potential risk groups are patients with a history of hepatic dysfunction or those with hepatic failure at the initiation of treatment with nicardipine. Nicardipine should be used with particular caution in patients with hepatic failure.

### *Renal failure*

Nicardipine should be used with caution in patients with renal failure (see "Pharmacokinetics").

### *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 intracranial hypertension*

Nicardipine should be used with caution in patients with a risk of increased 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 medicinal products is not recommended in ischaemic 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 for use

#### *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 dosage of the beta-blocker should be individualized to the clinical situation (see "Interactions").

### *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 injection site irritation. The use of a central venous line or of a greater dilution of the solution could reduce the risk of occurrence of injection site reaction.

### *Paediatric 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 (see "Dosage/Administration").

This product contains 500 mg of sorbitol per 10 mL ampoule. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The sorbitol content in oral medications may affect the bioavailability of other concomitantly administered oral medications. Patients with hereditary fructose intolerance (HFI) should not receive this medication except as necessary. A detailed history of HFI symptoms should be obtained for each patient before prescribing this medication.

This medication contains less than 1 mmol (23 mg) of sodium per 10 mL ampoule, i.e., it is essentially "sodium-free".

## **Interactions**

### *Inadvisable combinations*

#### *Dantrolene*

Dantrolene administered by infusion:

In animal studies, fatal ventricular fibrillation cases are consistently observed when verapamil and dantrolene are administered intravenously. The combination of a calcium channel inhibitor and dantrolene is therefore potentially dangerous.

However, a few patients received the combination of nifedipine and dantrolene without any inconvenience.

### *Combinations requiring precautions for use*

#### *Idelalisib*

Increased adverse effects of nicardipine, such as orthostatic hypotension, especially in elderly patients.

Clinical monitoring and dosage adjustment of nicardipine should be performed during treatment with idealisib and after its discontinuation.

#### *Cyclosporine, tacrolimus and sirolimus*

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

### *CYP3A4 inducers and inhibitors*

Nicardipine is metabolised 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 due to its increased hepatic metabolism.

Clinical monitoring and possible dosage adjustment of nicardipine should be performed during treatment with the anticonvulsant and after its discontinuation.

Co-administration of potent CYP3A4 enzyme-inhibiting agents (e.g. cimetidine, clarithromycin, cobicistat, erythromycin, itraconazole, grapefruit juice, ketoconazole, nelfinavir, posaconazole, ritonavir, telaprevir, telithromycin, voriconazole) may cause an increase in the plasma concentrations of nicardipine.

Increased adverse effects of nicardipine, more commonly orthostatic hypotension, especially in elderly patients. Co-administration of calcium channel blockers with itraconazole has shown an increased risk of adverse effects, in particular oedema due to a decreased metabolism of the calcium channel blocker in the liver.

Clinical monitoring and dosage adjustment of nicardipine should be performed during treatment with a potent CYP3A4 enzyme inhibitor and after its discontinuation.

### *Combinations to be taken into account*

#### *Potential additive antihypertensive effect*

Medicinal products which could potentiate the antihypertensive effect of nicardipine during concomitant administration, with an increased risk of orthostatic hypotension, include baclofen, urologic alpha-blockers (alfuzosin, doxazosin, prazosin, silodosin, tamsulosin, terazosin), alpha-blocking antihypertensive agents (doxazosin, prazosin, urapidil), tricyclic antidepressants, imipramine antidepressants, neuroleptics, opioids and amifostine.

#### *Nitrate derivatives and related agents*

Increased risk of hypotension, particularly orthostatic hypotension.

#### *Medicinal products that cause orthostatic hypotension*

Increased risk of hypotension, particularly orthostatic hypotension.

#### *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.

### *Enhancement of negative inotropic effect*

Nicardipine may enhance the negative inotropic effect of beta-blockers in cardiac failure (bisoprolol, carvedilol, metoprolol, nebivolol) and may cause hypotension, cardiac failure in patients with latent or uncontrolled cardiac failure (see “Warnings and precautions”). Moreover, the presence of a beta-blocker treatment can minimise the reflex sympathetic reaction set into action in case of excessive haemodynamic repercussion.

Nicardipine may enhance the negative inotropic effect of beta-blockers (except for esmolol) and may cause hypotension, cardiac failure in patients with latent or uncontrolled cardiac failure (see “Warnings and precautions”) (addition of negative inotropic effects). Moreover, the beta-blocker can minimise the reflex sympathetic reaction set into action in case of excessive haemodynamic repercussion.

### *Magnesium*

Due to the possible risk of pulmonary oedema or excessive decrease in blood pressure, caution should be taken if magnesium sulphate is used concomitantly (see “Warnings and precautions”).

### *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.

### *Decrease of antihypertensive effect*

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

### *Competitive neuromuscular blockers*

Limited data suggest that nicardipine, as other calcium channel blockers, enhances neuromuscular block possibly by acting at the post-synaptic 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.

## **Pregnancy, lactation**

### *Pregnancy*

Animal studies have shown no teratogenic effects. In the absence of teratogenic effects in animals, no malformative effect is expected in humans. In fact, until now, substances responsible for malformations in humans have always been demonstrated to be teratogenic in animals during studies carried out well in two species. Nicardipine should only be used if the benefit outweighs the risk because a reduction of birth weight in newborns has been reported when used in combination with calcium channel blockers.

Limited pharmacokinetic data have shown that nicardipine IV 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 foetotoxic 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 oedema has been observed when nicardipine has been used as tocolytic during pregnancy (see “Warnings and precautions” and “Undesirable effects”), 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 cardio-vascular condition, except if there is no other acceptable alternative.

### *Lactation*

Nicardipine should not be used during breast-feeding (see “Preclinical data”).

### *Fertility*

Not applicable.

### **Effects on ability to drive and use machines**

Reactions to the medicinal product, which vary from one individual to another, may affect the ability to drive and use machines. More particularly at the beginning or in case of any change to treatment and in combination with alcohol. Precautions should be taken since the hypotensive effects of this medicinal product may cause dizziness.

### **Undesirable effects**

#### Summary of the safety profile

The majority of undesirable effects are the consequence of the vasodilator effects of nicardipine. The most common effects are headache, dizziness, peripheral oedema, palpitations and flushing.

#### Tabulated list of adverse reactions

Adverse reactions listed below have been observed during clinical studies and/or after marketed use and are based on clinical trial data and classified according to MedDRA System Organ Class.

Frequency categories are defined according to the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  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 disorders	Not known – anaphylactic reaction

## Product information for human medicinal products

Nervous system disorders	Very common – headache
	Common – dizziness
Cardiac disorders	Common – lower limb oedema, palpitations
	Common – hypotension, tachycardia
	Not known – atrioventricular block, angina pectoris
Vascular disorders	Common – orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Not known – pulmonary oedema*
Gastrointestinal disorders	Common – nausea, vomiting
	Not known – paralytic ileus
Hepatobiliary disorders	Not known – hepatic enzyme increased
Skin and subcutaneous tissue disorders	Common – flushing
	Not known – erythema
General disorders and administration site conditions	Not known – phlebitis

\*cases have been also reported when used as tocolytic during pregnancy (see “Pregnancy, lactation”).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the EIViS portal (Electronic Vigilance System). You can obtain information about this at [www.swissmedic.ch](http://www.swissmedic.ch).

### Overdose

#### *Signs and symptoms*

Overdose with nifedipine hydrochloride can potentially result in the following symptoms: marked hypotension, bradycardia, palpitations, flushing, drowsiness, collapse, peripheral oedema, confusion, slurred speech and hyperglycaemia. In animals, overdose also resulted in reversible hepatic function abnormalities, sporadic focal hepatic necrosis and progressive atrio-ventricular 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.

Nifedipine is not dialyzable.

### Properties/Effects

*ATC code*

C08CA04

*Mechanism of action*

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).

*Pharmacodynamics*

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.

*Clinical efficacy*

No data available.

### Pharmacokinetics

*Absorption*

No data available.

*Distribution*

Nicardipine is highly bound to plasma proteins over a wide concentration range.

*Metabolism*

Nicardipine is metabolised 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.

### *Elimination*

After co-administration of a radioactive intravenous dose of nifedipine with an oral 30 mg dose given every 8 hours, 49% of the radioactivity was recovered in the urine and 43% in the faeces within 96 hours. None of the dose was recovered as unchanged nifedipine in the urine. The elimination profile of the medicinal product 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 failure

The pharmacokinetics of intravenously administered nifedipine was studied in subjects with severe renal failure requiring haemodialysis (creatinine clearance <10 ml/min), mild/moderate renal failure (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 failure 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 function.

### **Preclinical data**

Nifedipine has been shown to pass into the milk of lactating animals. It has been reported in animal studies that the medicinal product is excreted into breast milk. In animal studies where this medicinal product was administered at a high dose during the terminal stage of pregnancy, an increase in foetal deaths, delivery disturbances, decrease in the body weight of offspring, and suppression of post-natal body weight gain were reported. However, toxicity to reproduction has not been reported.

### **Other information**

#### *Incompatibilities*

There is a risk of precipitation with products in solution of pH greater than 6 (e.g. bicarbonate solution, Ringer's solution, diazepam, furosemide, methohexital sodium, thiopental).

In the presence of saline solutions, there is a risk of nifedipine absorption on the plastic materials of infusion devices.

#### *Shelf life*

Do not use this medicine after the expiry date ("EXP") stated on the pack.

#### *Shelf life after opening*

The physicochemical stability of the undiluted solution or diluted in a solution of 5% glucose in a polypropylene syringe has been demonstrated for 24 hours at a temperature of +25°C, away from light.

Nevertheless, from a microbiological standpoint, the product should be used immediately.

### *Special precautions for storage*

Store at room temperature (15-25°C) in the original packaging, protected from light and out of the reach of children.

### *Instructions for handling*

1. Hold the ampoule with the coloured spot right up. If there is any liquid in the upper part of the ampoule, tap it to allow the liquid to run into the body of the ampoule.
2. Then grasp the top of the ampoule (above the tip) and apply a pressure to break the ampoule.

### **Authorisation number**

67'680 (Swissmedic).

### **Packs**

Nicardipin Labatec, ampoule 10 mg / 10 mL : 10 (A).

### **Marketing authorisation holder**

Labatec Pharma SA, 1217 Meyrin (GE)

### **Date of revision of the text**

*Foreign reference product: January 2019.*

*Without addition of safety relevant information by Swissmedic: October 2020.*