Annex III

Summary of Product Characteristics and Package Leaflet

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

To be completed nationally

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

To be completed nationally

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

To be completed nationally

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Intravenous nicardipine [or invented name] 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

4.2 Posology and 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.

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 (see section 6.2 for details of compatible solutions)

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 affect. 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 100mg/day, in 2 daily doses. [To be completed nationally if applicable]

Older 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.

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. (See sections 4.4, 4.6 and 4.8)

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.

Paediatric 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 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 posology should be used.

4.3 Contraindications

Known hypersensitivity to nicardipine or to any of the excipients listed in section 6.1

Severe aortic stenosis

Compensatory hypertension, i.e. in case of an arteriovenous shunt or aortic coarctation

Unstable angina

Within 8 days after myocardial infarction

4.4 Special warnings and precautions for use

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.

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 impairment and in pregnancy

Cardiac failure

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

Ischaemic cardiovascular disease.

Nicardipine is contra-indicated in unstable angina and immediately following myocardial infarction (see section 4.3)

Nicardipine should be used with caution in patients with suspected coronary ischemia. 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

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 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 posology of the beta blocker should be individualized to the clinical situation. (See section 4.5)

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.

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 (refer to section 4.2)

[Product specific formulation warnings to be completed nationally]

4.5 Interaction with other medicinal products and other forms of interaction

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 (see section 4.4)

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 oedema or excessive decrease in blood pressure, caution should be taken if magnesium sulphate is used concomitantly (see section 4.4)

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 oedema due to a decreased metabolism of the calcium channel blocker in the liver.

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, opiods 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.

4.6 Fertility, 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 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 section 4.8), 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 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.

Fertility

No data

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Summary of the safety profile

The majority of undesirable effects are the consequence of the vasodilator effects of nicardipine. The most frequent events 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 during 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 (≥ 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
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 section 4.6)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [national reporting system]

4.9 Overdose

Symptoms

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

Management

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic class: selective calcium inhibitors with vascular effects, ATC code: C08CA04

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.

5.2 Pharmacokinetic properties

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 coadministration 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 administration of nicardipine was studied in subjects with severe renal dysfunction requiring hemodialysis (creatinine clearance < 10 ml/min), mild/moderate renal dysfunction (creatinine clearance 10 - 50 mi/min) and normal renal function (creatinine clearance >50 ml/min). At steady state, Cmax and AUC were significantly higher and clearance significantly lower in subjects with mild/moderate renal dysfunction 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 (see section 4.4)

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

To be completed nationally

6.2 Incompatibilities

To be completed nationally

6.3 Shelf life

To be completed nationally

6.4 Special precautions for storage

To be completed nationally

6.5 Nature and contents of container

To be completed nationally

6.6 Special precautions for disposal and other handling

To be completed nationally

7. MARKETING AUTHORISATION HOLDER

To be completed nationally

8. MARKETING AUTHORISATION NUMBERS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally

10. DATE OF REVISION OF THE TEXT

To be completed nationally

PACKAGE LEAFLET

Package leaflet: Information for the patient

[Product name]

Nicardipine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Nicardipine solution for injection is and what it is used for
2. What you need to know before you take Nicardipine solution for injection
3. How to take Nicardipine solution for injection
4. Possible side effects
5. How to store Nicardipine solution for injection
6. Contents of the pack and other information

1. What Nicardipine solution for injection is and what it is used for

Nicardipine solution for injection contains nicardipine hydrochloride, which belongs to a group of medicines called calcium channel blockers.

Nicardipine solution for injection is used to treat very severe high blood pressure. It can also be used to control high blood pressure after an operation.

2. What you need to know before you take Nicardipine solution for injection

Do not take Nicardipine solution for injection

- If you are allergic to nicardipine or any of the other ingredients of this medicine (listed in section 6)
- If you have chest pain
- If your high blood pressure is because of narrowing of a heart valve or other defects in the heart
- If you have had a heart attack in the last eight days

Warnings and precautions

Your doctor will take special care:

- If you have heart failure
- If you have angina
- If your liver is not working properly, or you have had liver disease in the past
- If you have high pressure in the brain
- If you have suffered a recent stroke
- If you are taking beta-blockers
- If you are pregnant
- If you are under 18 years of age

If you have these conditions, your doctor may need to monitor additional tests or change the dose. If any of the above apply to you, or you are not sure, tell your doctor before receiving **Nicardipine solution for injection**

Other medicines and Nicardipine solution for injection

Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines. This is because Nicardipine solution for injection can affect the way some other medicines work. Also, some other medicines can affect the way Nicardipine solution for injection works.

In particular, tell your doctor if you are taking any of the following medicines:

- Dantrolene (used to treat long-term muscle stiffness)
- Beta-blockers (used to treat high blood pressure and heart conditions) such as propranolol, atenolol and metoprolol
- Medicines used to control seizures, such as carbamazepine , phenobarbitone, primidone and phenytoin
- Baclofen (used to treat muscle spasms)
- Medicines used to control the body's immune system, such as tacrolimus, sirolimus and ciclosporin
- Itraconazole (used to treat certain types of fungal infection)
- Rifampicin (used to treat tuberculosis and certain other types of infection)
- Alpha-blockers (used to treat high blood pressure, or prostate problems in men) such as doxazosin, prazosin and terazosin
- Any other medicine for high blood pressure
- Cimetidine (to treat indigestion or stomach ulcers)
- Digoxin (used for heart conditions)
- Amifostine (used to protect against the harmful effects of certain cancer treatments)
- Medicines to treat depression, anxiety or other mental health problems
- Strong painkilling medicines like morphine or codeine
- Medicines used to treat inflammation such as steroids and tetracosactide
- Magnesium injection (used to treat severe high blood pressure in pregnancy)

If you are having an operation, your anaesthetist will need to know which other medicines you are taking, as some of these can affect the way Nicardipine solution for injection works.

Do not drink grapefruit juice or eat grapefruit whilst taking this medication as it may increase the blood levels of nicardipine

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Formulation specific warnings to be added here, if applicable

3. How to take Nicardipine solution for injection

This medicine will be given to you in hospital.

Your doctor will decide on the amount of Nicardipine solution for injection you will be given. This will depend on much and how fast they want to reduce your blood pressure by.

The medicine will be injected slowly into a vein. Your blood pressure will be taken whilst you are receiving treatment and the dose adjusted to make sure you have a fall in your blood pressure to normal levels.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

Nicardipine solution for injection will be given to you by a doctor, who will ensure that the correct dose is given for your condition. If you have any concerns tell your doctor or nurse

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Headache is the most common side effect, and may affect more than 1 in 10 people.

Other common side effects (these may affect up to 1 in 10 people) are:

Dizziness
Swollen legs or ankles
Increased heart rate, feeling your heart beat (palpitations)
Low blood pressure, especially on standing up. This may cause dizziness, lightheadednesss or fainting
Feeling sick or being sick
Flushing of the skin

Other side effects

(Frequency unknown)

Reduction in blood platelets, which may increase the risk of bleeding or bruising
Slow heart rhythm
Chest pain
Heart problems leading to increased fluid in the lungs and shortness of breath
Abdominal pain
Redness of the skin
Inflammation of the vein where the medicine has been given
Changes in blood tests of how your liver is working

If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Nicardipine solution for injection

You hospital will store this medicine appropriately

6. Contents of the pack and other information

What Nicardipine solution for injection contains

The active substance is nicardipine. Each [to be completed nationally] contains [to be completed nationally]

The other ingredients are: [to be completed nationally]

What Nicardipine solution for injection looks like and contents of the pack

Nicardipine solution for injection is a clear colourless solution. It is available in [to be completed nationally] containing [to be completed nationally]

Each pack contains [to be completed nationally]. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
[to be completed nationally]

Manufacturer:
[to be completed nationally]

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

[to be completed nationally]

This leaflet was approved in {month YYYY}.