SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nicardipine 1 mg/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 1 mg of nicardipine hydrochloride.
Each 10 ml ampoule contains 10 mg of nicardipine hydrochloride.

Excipients with known effect

This medicinal product contains sodium.
Each ml of solution contains 0.039 mg equivalent to 0.0017 mmol of sodium.
Each 10 ml ampoule contains 0.39 mg equivalent to 0.017 mmol of sodium.

Each ml of solution contains 50 mg sorbitol (E420).
Each 10 ml ampoule contains 500 mg sorbitol (E420).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion (infusion).
Clear, pale yellow colour solution.
pH 3.2 – 3.8
Osmolality 280 – 320 mOsm/Kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of 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.

Posology

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 20 mg 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.

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 4 mg/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.

Method of administration
Nicardipine should be administered by continuous intravenous infusion only.

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.

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

It is recommended to administer nicardipine with caution to avoid an excessive drop in blood pressure. Indeed, 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. As some cases of acute pulmonary oedema have been reported during pregnancy, nicardipidine should be administered with caution in pregnant women, and these should be closely monitored for the possible development of acute pulmonary oedema. In case of acute pulmonary oedema, nicardipine should be stopped immediately, and appropriate treatment should be initiated.

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. Nicardipine should be used with caution in patients with hepatic impairment.

Renal failure

Nicardipine should be used with caution in patients with renal impairment (see section 5.2).

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

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 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 (see section 4.2).

Excipient

This medicine contains sorbitol. Patients with hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary.

4.5 Interaction with other medicinal products and other forms of interaction

Unadvised combinations

Dantrolene

With dantrolene administered via infusion:
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. However, some patients received the association nifedipine and dantrolene without harm.

Combinations subject to precautions for use

Idelalisib

Increase in the adverse effects of nicardipine, such as orthostatic hypotension, especially in the elderly.
Clinical monitoring and dose adjustment of nicardipine during treatment with idelalisib and after discontinuation.

Immunosuppressants (ciclosporin, everolimus, sirolimus, tacrolimus, temsirolimus)

Increase in blood levels of the immunosuppressant, by inhibiting its metabolism.
Determination of blood levels of the immunosuppressant, monitoring of renal function and adjustment of its dosage during treatment and after discontinuation.

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 by increasing its hepatic metabolism.
Clinical monitoring and possible adjustment of the dosage of nicardipine during treatment with the anticonvulsant and after its discontinuation.
Co-administration of CYP3A4 enzyme-inhibiting agents (such as cimetidine, clarithromycin, cobicistat, erythromycin, itraconazole, grapefruit juice, ketoconazole, nelfinavir, posaconazole, ritonavir, telaprevir, telithromycin, voriconazole) may cause an increase in the plasma concentrations of nicardipine.
Increase in the adverse effects of nicardipine, most often hypotension type, especially in the elderly.
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.
Clinical monitoring and dosage adjustment of nicardipine during treatment with and after discontinuation of the potent enzyme inhibitor of CYP3A4.

Combinations to be taken into account

Potential additive antihypertensive effect

Concomitant medications which could potentiate the antihypertensive effect of nicardipine, with an increased risk of orthostatic hypotension, include baclofen, alpha-blockers for urological purposes (alfuzosin, doxazosin, prazosin, silodosin, tamsulosin, terazosin), alpha-blocker antihypertensive drugs (doxazosin, prazosin, urapidil), tricyclic antidepressants, imipramine antidepressants, neuroleptics, opiods and amifostine

Nitrated and related derivatives

Increased risk of hypotension, especially orthostatic.

Drugs causing orthostatic hypotension

Increased risk of hypotension, especially orthostatic.

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 heart failure (bisoprolol, carvedilol, metoprolol, nebivolol) and may cause hypotension, heart failure in patient with latent or uncontrolled heart failure (see section 4.4). The presence of beta-blocker therapy may also minimize the sympathetic reflex response to excessive hemodynamic repercussions.

Nicardipine may increase the negative inotropic effect of beta-blockers (except esmolol) and lead to hypotension, heart failure in patients with latent or uncontrolled heart failure (see section 4.4) (addition of negative inotropic effects). The beta-blocker can also minimize the sympathetic reflex reaction involved in the event of excessive hemodynamic repercussions.

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).

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-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

Studies in animals have not shown any evidence of a teratogenic effect. In the absence of a teratogenic effect in animals, a malformative effect in humans is not expected. Indeed, to date, the substances responsible for malformations in the human species have been shown to be teratogenic in animals during well-conducted studies on two species. Nicardipine should only be used if the benefit outweighs the risk as reduced birth weight in newborns has been reported in combination with calcium channel blockers.
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 sections 4.4 and 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.

Breast-feeding

Nicardipine should not be used during breast-feeding (see section 5.3).

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Reactions to the drug, which vary from person to person, can affect your ability to drive or use machines. More particularly at the start or in case of modification of the treatment as well as in combination with alcohol. Caution should be taken as the hypotensive effects of this medication can cause dizziness.

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	Adverse reactions
Blood and lymphatic system disorders	Not known	Thrombocytopenia
Immune system disorders	Not known	Anaphylactic reaction
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	Hypotension, orthostatic hypotension
	Not known	Flushing
Respiratory, thoracic and mediastinal disorders	Not known	pulmonary oedema*
Gastrointestinal disorders	Common	Nausea, vomiting
	Not known	Paralytic ileus
Skin and subcutaneous tissue disorders	Not known	Erythema, cutaneous rash
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 (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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 group: SELECTIVE CALCIUM INHIBITORS WITH VASCULAR EFFECTS,
ATC code: C08CA04 (cardiovascular system).

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).

Pharmacodynamic effects
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.

Biotransformation

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.

Elimination

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 ml/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 dysfunction (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

Sorbitol (E420),
citric acid monohydrate,
sodium citrate,
hydrochloric acid,
sodium hydroxide,
water for injections.

6.2 Incompatibilities

A risk of precipitation exists with products presenting a pH in solution greater than 6 (for example, bicarbonate solution, Ringer's solution, diazepam, furosemide, sodium methohexital, thiopental).
A risk of adsorption of nicardipine exists on plastic materials in devices for infusion in the presence of saline solutions.

This medicinal product should not be mixed with other medicinal products except those mentioned under section 6.6.

6.3 Shelf life

Before opening: 2 years.

After opening:

The physical-chemical stability of the undiluted solution or diluted in a solution of 5% dextrose in a polypropylene syringe has been demonstrated for 24 hours at temperatures of +25°C, away from light.

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

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original container in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 ml in a type I brown glass ampoule with an OPC (One Point Cut) break system. Boxes of 5, 10 or 50 ampoules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Method of use for opening the ampoules

1. Hold the ampoule, pointing the colour point upward. If liquid is in the upper part of the ampoule, tap on the ampoule to make it descend into the body of the ampoule.
2. Then grasp the end of the ampoule (above the point) and exert pressure to break the ampoule.

Instructions on dilution

The miscibility of Nicardipine has been tested with the following infusion fluids:

- 0.45% sodium chloride,
- 0.9% sodium chloride,
- 5% dextrose,
- 5% dextrose in 0.45% sodium chloride,
- 5% dextrose in 0.9% sodium chloride or
- 5% dextrose in 40 mM potassium chloride.

The compatibility of diluted Nicardipine was tested in polypropylene container and PVC-free infusion bag.

Comment [CC1]: Info ajoutée lors de la phase nationale stab in use non approuvée au UK à date

Comment [CC2R1]: Si variation stab in use approuvée ne pas soumettre

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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1 rue Alexander Fleming

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FRANCE

8 MARKETING AUTHORISATION NUMBER(S)

PL 14434/0047

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/04/2014

10 DATE OF REVISION OF THE TEXT

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