SCHEDULING STATUS S3

1. NAME OF THE MEDICINE

NICARDIPINE EQUITY 10 mg

Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains nicardipine hydrochloride 10 mg per 10 ml

Excipient(s) with known effect:

Contains sugar: Sorbitol 500 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection

Clear and yellow coloured solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NICARDIPINE EQUITY is indicated only 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 medicines are not recommended or are contraindicated

NICARDIPINE EQUITY is also indicated for the treatment of postoperative hypertension.

4.2 Posology and method of administration

Posology

NICARDIPINE EQUITY should only be administered by medical practitioners experienced in haemodynamic management and only be used in intensive care, high care and interoperative settings. Blood pressure and heart rate must be continuously monitored.

The speed of administration must be accurately controlled using 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 EQUITY.

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 EQUITY 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 medicine: Discontinue NICARDIPINE EQUITY or titrate downward while appropriate oral therapy is established. When an oral antihypertensive medicine is being instituted, consider the lag time of onset of the oral medicine's affect. Continue blood pressure monitoring until desired effect is achieved.

Geriatrics

The safety and efficacy in patients over 65 years has not been established.

Paediatric population

The safety and efficacy in low birth weight infants, new-borns, nursing infants, infants and children has not been established.

Pregnancy (Severe Pre-eclampsia)

The safety and efficacy have not been established

A syndrome of high blood pressure, fluid accumulation in the tissues

and protein in the urine that becomes apparent in the second half of pregnancy. Pre-eclampsia is primarily a placental disorder with damage to the inner lining of placental blood vessels.

Hepatic impairment

NICARDIPINE EQUITY should be used with caution in these patients. Since NICARDIPINE EQUITY is metabolised in the liver, lower dose regimen in patients with impaired liver function.

Renal Impairment

Lower dose regimen in patients with renal impairments

Method of administration

NICARDIPINE EQUITY should be administered by continuous intravenous infusion only.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1
- Mitral valve stenosis and severe aortic stenosis including aortic valve stenosis
- Compensatory hypertension, i.e., in case of an arteriovenous shunt or aortic coarctation
- Unstable angina
- Within 8 days after myocardial infarction
- Patients with rare hereditary problems of fructose intolerance should not receive this medicine.

4.4 Special warnings and precautions for use

Rapid pharmacologic reductions in blood pressure may produce severe systemic hypotension including diminished organ perfusion and reflex tachycardia. If either occurs with NICARDIPINE EQUITY consider decreasing the dose by half or stopping the infusion.

Bolus administration or intravenous administration not controlled is contraindicated. Infusion must be administered only through electronic syringe driver of a volumetric pump is not recommended and can increase the risk of serious hypotension.

Moderate to severe Cardiac failure

NICARDIPINE EQUITY should be used with extreme 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 EQUITY is contraindicated in unstable angina and immediately following myocardial infarction (refer to section 4.3).

NICARDIPINE EQUITY 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 EQUITY dosage, or during the course of treatment.

Pregnancy

There is a risk of severe maternal hypotension and potentially fatal foetal hypoxia. Concomitant use of NICARDIPINE EQUITY with magnesium sulphate is contraindicated.

Patients with history of hepatic dysfunction or impaired hepatic function.

Rare cases of abnormal hepatic function possibly associated with the use of NICARDIPINE EQUITY 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 EQUITY.

Patients with portal hypertension

The worsening portal vein hypertension and portal-systemic collateral blood flow index in cirrhotic patients have been reported with NICARDIPINE EQUITY.

Patients with pre-existing elevated intracranial pressure

Intracranial pressure must be monitored, to allow calculation of the cerebral perfusion pressure.

Patients with stroke

NICARDIPINE EQUITY should not be used with a recent history of stroke.

Combination with beta-blockers

Caution should be exercised when using NICARDIPINE EQUITY in combination with a beta-blocker in patients with decreased cardiac function. In such case, the dosage of the beta-blocker should be individualised to the clinical situation (refer to 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 EQUITY has not been established.

Excipient warnings

This product contains sorbitol. Patients with rare hereditary problem of fructose intolerance should not be given NICARDIPINE EQUITY (see section 4.3).

4.5 Interactions with other medicines and other forms of interaction

Enhancement of negative inotropic effect

NICARDIPINE EQUITY may enhance the negative inotropic effect of beta-blockers and may cause heart failure in patients with latent or uncontrolled heart failure (refer to section 4.4)

Dantrolene

The combination of a calcium channel inhibitor such as NICARDIPINE EQUITY and dantrolene is therefore potentially dangerous and is contraindicated.

Magnesium

Concomitant use of NICARDIPINE EQUITY with magnesium is contraindicated.

CYP3A inducers and inhibitors

NICARDIPINE EQUITY is metabolised by cytochrome P450 3A4. Co-administration of CYP3A4 enzyme-inducing medicines (e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone and rifampicin) may cause a decrease in the plasma concentrations of NICARDIPINE EQUITY.

Co-administration of CYP3A4 enzyme-inhibiting medicines (e.g., cimetidine, itraconazole and grapefruit juice) may cause an increase in the plasma concentration of NICARDIPINE EQUITY**.** Co-administration of NICARDIPINE EQUITY 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.

Cyclosporine, tacrolimus and sirolimus

Concomitant administration of NICARDIPINE EQUITY and cyclosporin, tacrolimus or sirolimus may result in elevated plasma ciclosporin/tacrolimus levels. Blood levels should be monitored and dosage of immunosuppressant and/or NICARDIPINE EQUITY should be reduced, if required.

Digoxin

NICARDIPINE EQUITY has been reported to increase the plasma levels of digoxin. Digoxin levels should be monitored when concomitant therapy with NICARDIPINE EQUITY is initiated.

Potential additive antihypertensive effect

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

Decrease of antihypertensive effect

NICARDIPINE EQUITY 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 EQUITY 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.

Competitive neuromuscular blockers

Nicardipine may enhance neuromuscular block possibly by acting at the post-junctional region. Neuromuscular block infusion dose requirements could be reduced by the concurrent use of NICARDIPINE EQUITY Reversal of neuromuscular block by neostigmine appears not to be affected by NICARDIPINE EQUITY infusion. No additional monitoring is required.

4.6 Fertility, pregnancy and lactation

Pregnancy

Limited pharmacokinetic data have shown that NICARDIPINE EQUITY does not accumulate and has a low placental transfer.

In clinical practice the use of NICARDIPINE EQUITY during the first two trimesters in a limited number of pregnancies has not revealed any malformities or particular foetotoxic effect to date.

The use of NICARDIPINE EQUITY for severe pre-eclampsia during the third trimester of pregnancy could produce a tocolytic effect.

Breastfeeding

NICARDIPINE EQUITY and its metabolites are excreted in human milk. Mother on treatment with NICARDIPINE EQUITY must not breastfeed their babies.

Fertility

No data on male and female fertility is available

4.7 Effects on ability to drive and use machines

NICARDIPINE EQUITY has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

Most undesirable effects are the consequence of the vasodilator effects of NICARDIPINE EQUITY**.** The most frequent side effects are headache, dizziness, peripheral oedema, palpitations and flushing.

b. Tabulated summary of adverse reactions

Adverse reactions listed below are classified according to MedDRA System Organ Class (SOC). 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	**Very common**	**Common**	**Not known**
Blood and the lymphatic system disorders			Thrombocytopenia
Metabolism and nutrition disorders			Hypophosphatemia
Psychiatric disorders			Lethargy, mood disturbances
Nervous system disorders	Headache	Dizziness	Migraine, confusion, hypertonia
Eye disorders			Visual disturbances, eye pain, conjunctivitis
Ear and labyrinth disorders			Tinnitus

Cardiac disorders		Lower limb oedema, palpitations, hypotension, tachycardia	Atrioventricular block, angina pectoris, ST segment depression, inverted T wave
Vascular disorders		Orthostatic hypotension	Deep-vein thrombophlebitis, excessive fall in blood pressure which leads to cerebral or myocardial ischaemia or transient blindness
Respiratory, thoracic and mediastinal disorders			Pulmonary oedema*, respiratory disorder
Gastrointestinal disorders		Nausea, vomiting	Paralytic ileus, constipation, dyspepsia
Hepato-biliary disorders			Hepatic enzyme increased (liver function abnormalities)
Skin and subcutaneous tissue disorders		Flushing	Erythema, gingival hyperplasia, rash, pruritus
Musculoskeletal, connective tissue and bone disorders			Myalgia, tremor
Renal and urinary disorders			Micturition disorders including increased frequency
Reproductive system and breast disorders			Gynecomastia, impotence
General disorders and administrative site conditions			Phlebitis, fever

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8}

4.9 Overdose

Symptoms

Overdose with NICARDIPINE EQUITY can potentially result in marked hypotension, bradycardia, palpitations, flushing, drowsiness, collapse, peripheral oedema, confusion, slurred speech and hyperglycaemia. Based on reports in laboratory animals, overdosage also resulted in reversible hepatic function abnormalities, sporadic focal hepatic necrosis and progressive atrioventricular 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 EQUITY is not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective calcium inhibitors with vascular 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 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, because of a decrease in after-load, cardiac output is markedly and durably increased.

Vasodilator action 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

Absorption

Following intravenous administration, nicardipine is rapidly absorbed with the time to onset ranging from 5 to 15 minutes. Peak plasma levels can reach 184 ng/ml and steady state plasma concentrations of 157 ng/ml are achieved within 24 to 48 hours of continuous infusion.

Distribution

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

Metabolism

Nicardipine is metabolised by cytochrome P450 3A4. Less than 0,03 % of unchanged nicardipine is recovered in the urine after oral or intravenous single dose administration or multiple dose administration of 3 times daily for 3 days. The most abundant metabolite in urine is the glucuronide of the hydroxyl form, which is formed by the oxidative cleaving of the N-methylbenzyl moiety and the oxidation of the pyridine ring.

Excretion/Elimination

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

The elimination profile of nicardipine following an intravenous dose consists of three phases, with corresponding half-life: distribution 6,4 min, elimination 1,5 hours, terminal elimination 7,9 hours. A clinical offset of action of approximately 15 minutes has been reported.

Renal impairment

At steady state, C_{max} and AUC were significantly higher and clearance significantly lower in subjects with moderate to severe renal impairment (creatinine clearance 10 – 50 ml/min) compared to subjects with normal renal function (creatinine clearance > 50 ml/min). There was no significant difference in the main pharmacokinetic parameters between severe impairment of renal function (creatinine clearance < 10 ml/min) and normal renal function (refer to 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 medicine is excreted into breast milk. In animal experiments where this medicine 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 postnatal body weight gain were reported. However, toxicity to reproduction has not been reported.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol

Citric acid monohydrate

Sodium citrate

Hydrochloric acid

Sodium hydroxide

Water for injections

Nitrogen

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines except those mentioned under section 4.2.

6.3 Shelf life

Before opening: 24 months

After opening: The physicochemical stability of the undiluted solution or diluted in a solution of 5 % dextrose in water 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

Store at or below 25 °C.

The ampoules must be kept in the outer carton in order to protect them from light.

Not for use undiluted.

Store all medicines out of reach of children.

6.5 Nature and contents of container

Neutral type I borosilicate coloured (brown), opaque glass ampoules with a capacity of 10 ml, the ampoules are packaged in thermoformed blisters strips or in paper racks placed inside cardboard boxes.

Pack size: 5, 10 and 50 ampoules in outer carton

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd.

100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive, Irene,

Pretoria, 0157

8. REGISTRATION NUMBER(S)

Nicardipine Equity: 52/7.1/0487

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 October 2021

10. DATE OF REVISION OF THE TEXT

18 September 2023