Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nicorandil 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Nicorandil 10mg
Excipient(s) with known effect:
Each tablet contains 10mg nicorandil.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet, white to off white, round, scored on one side and engraved with "10" on the other side.
The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Nicorandil 10mg Tablets are indicated in adults for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or have a contraindication or intolerance to first-line antianginal therapies (such as beta-blockers and/or calcium antagonists).

4.2 Posology and method of administration

Posology
The usual therapeutic range is 10 to 20 mg twice daily. The usual starting dose is 10 mg twice daily (bid), in the morning and in the evening preferably. It is recommended that the dose be titrated upwards in accordance with the patient's needs, response and tolerance up to 40 mg twice daily, if necessary. A lower starting dose of 5 mg twice daily may be used in patients particularly prone to headache.
Elderly: There are no special dose requirements for elderly patients, but as with all medicines, use of the lowest effective dose is recommended.
Patients with liver and/or renal impairment
There are no special dosage requirements for patients with liver and/or renal impairment.
Paediatric population: Nicorandil Tablets are not recommended in paediatric patients since its safety and efficacy have not been established in this patient group.
Method of administration
Nicorandil Tablets are administered by oral route.
The tablets are to be swallowed in the morning and in the evening with a glass of water. The tablets should not be crushed or chewed.
The tablet can be divided into equal doses.
Administration is independent of food intake

4.3 Contraindications

• Hypersensitivity to nicorandil or to any of the excipients listed in section 6.1.
• Patients with shock (including cardiogenic shock), severe hypotension, or left ventricular dysfunction with low filling pressure or cardiac decompensation.
• Use of phosphodiesterase 5 inhibitors, since this can lead to a serious drop in blood pressure (see section 4.5).
• Use of soluble guanylate cyclase stimulator(s) (such as riociguat) since it can lead to a serious fall in blood pressure (see section 4.5).
• Hypovolaemia.
• Acute pulmonary oedema.

4.4 Special warnings and precautions for use

Ulcerations

Gastrointestinal ulcerations, skin and mucosal ulceration have been reported with nicorandil (see section 4.8).

Gastrointestinal ulcerations

Nicorandil induced ulceration may occur at different locations in the same patient. They are refractory to treatment and most only respond to withdrawal of nicorandil treatment. If ulceration(s) develops, nicorandil should be discontinued (see section 4.8). Healthcare professionals should be aware of the importance of a timely diagnosis of nicorandil-induced ulcerations and of a rapid withdrawal of nicorandil treatment in case of occurrence of such ulcerations. Based on available information, the time between starting nicorandil use and the onset of ulceration ranges from shortly after initiating nicorandil treatment to several years after starting nicorandil.

Gastrointestinal haemorrhage secondary to gastrointestinal ulceration has been reported with nicorandil. Patients taking acetylsalicylic acid or NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) concomitantly are at increased risk for severe complications such as gastrointestinal haemorrhage. Therefore caution is advised when concomitant use of acetylsalicylic acid or NSAIDs and nicorandil is considered (see section 4.5).

If advanced, gastrointestinal ulcerations may evolve into perforation, fistula, or abscess formation. Patients with diverticular disease may be at particular risk of fistula formation or bowel perforation during nicorandil treatment.

Gastrointestinal perforations in context of concomitant use of nicorandil and corticosteroids have been reported. Therefore, caution is advised when concomitant use is considered.

Eye ulcerations

Conjunctivitis, conjunctival ulcer and corneal ulcer have been reported with nicorandil. Patients should be advised of the signs and symptoms and monitored closely for corneal ulcerations. If ulceration(s) develops, nicorandil should be discontinued (see section 4.8).

Decrease of blood pressure

Caution is advised if nicorandil is used in combination with other medicinal products with blood pressure lowering effect (see sections 4.5 and 4.8).

Heart failure

Due to lack of data, caution is advised to use nicorandil in patients with heart failure class NHYA III or IV.

Hyperkalaemia

Severe hyperkalaemia has been reported very rarely with nicorandil. Nicorandil should be used with care in combination with other medical products that may increase potassium levels especially in patients with moderate to severe renal impairment (see sections 4.5 and 4.8).

Paediatric population

Nicorandil Tablets are not recommended in paediatric patients since its safety and efficacy have not been established in this patient group.

G6PD deficiency

Nicorandil Tablets should be used with caution in patients with glucose-6-phosphate dehydrogenase deficiency. Nicorandil acts in part through its organic nitrate moiety. The metabolism of organic nitrates can result in the formation of nitrites which may trigger methemoglobinaemia in patients with glucse-6-phosphate dehydrogenase deficiency.

Nicorandil Tablets contain less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

Concurrent use of nicorandil and phosphodiesterase 5 inhibitors, e.g. sildenafil, tadalafil, vardenafil, is contraindicated, since it can lead to a serious drop in blood pressure.

Concomitant use of soluble guanylate cyclase stimulators (such as riociguat) is contraindicated, since it can lead to a serious drop in blood pressure.

Therapeutic doses of nicorandil may lower the blood pressure of hypotensive patients.

If nicorandil is used concomitantly with antihypertensive agents or other medicinal products with blood pressure lowering effect (e.g. vasodilators, tricyclic antidepressants, alcohol), the blood pressure lowering effect may be increased.

Dapoxetine should be prescribed with caution in patients taking nicorandil due to possible reduced orthostatic tolerance.

Gastrointestinal perforations in the context of concomitant use of nicorandil and corticosteroids have been reported. Caution is advised when concomitant use is considered (see section 4.4).

In patients concomitantly receiving NSAIDs including acetylsalicylic acid for both cardiovascular prevention and anti-inflammatory doses, there is an increased risk for severe complications such as gastrointestinal ulceration, perforation and haemorrhage (see section 4.4).

Caution is advised when nicorandil is used in combination with other medical products that may increase potassium levels (see sections 4.4 and 4.8).

The metabolism of nicorandil is not significantly affected by cimetidine (a CYP inhibitor), or rifampicin (a CYP3A4 inducer). Nicorandil does not affect the pharmacodynamics of acenocoumarol.

4.6 Fertility, pregnancy and lactation

Pregnancy: There are no or limited amount of data from the use of nicorandil in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of Nicorandil Tablets during pregnancy.

Breast-feeding: Animal studies have shown that nicorandil is excreted in small amounts into the breast milk. It is not known whether nicorandil is excreted in human milk, therefore Nicorandil Tablets are not recommended during breastfeeding.

Fertility: There are insufficient data on fertility to estimate the risk for humans (see section 5.3)

4.7 Effects on ability to drive and use machines

Nicorandil Tablets have an influence on the ability to drive and use machines. Indeed, as with other vasodilators, blood pressure-lowering effects as well as dizziness and feeling weakness induced by nicorandil can reduce the ability to drive or to use machines. This effect can be increased in conjunction with alcohol or other medicinal products with blood pressure lowering effect (e.g. vasodilators, tricyclic antidepressants) (see section 4.5). Therefore, patients should be advised not to drive or use machines if these symptoms occur.

4.8 Undesirable effects

Summary of safety profile

The most common adverse reaction reported in clinical trials is headache occurring in more than 30% of patients, particularly in the first days of treatment and responsible for most of study withdrawal.

Progressive dose titration may reduce the frequency of these headaches (see section 4.2).

In addition, serious adverse reactions including ulcerations and their complications (see section 4.4) were reported during the post marketing surveillance of nicorandil.

Tabulated list of adverse reactions

The frequencies of adverse reactions reported with nicorandil are summarised in the following table by system organ class (in MedDRA) and by frequency. Frequencies are defined as:

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); Not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**

Infections and infestations		Abscess (skin abscess)*(see section 4.4)	Abscess (genital, anal or other gastrointestinal locations)* (see section 4.4)			
Metabolism and nutrition disorders					Hyperkalaemia (see sections 4.4 and 4.5)	
Nervous system disorders	Headache	Dizziness				IIIrd nerveparalysis, VIthnerve paralysis (often associated with headache)
Eye disorders			Corneal ulcer*, conjunctival ulcer, conjunctivitis (see section 4.4)			Diplopia Ophthalmoplegia (often associated with headache)
Cardiac disorders		Heart rate increased				
Vascular disorders		Cutaneous vasodilation with flushing	Decrease in blood pressure (see section 4.4)			
Gastrointestinal disorders		Diverticulitis*, gastrointestinal haemorrhage*, gastrointestinal ulcerations (stomatitis, aphthosis, mouth ulcer, tongue ulcer, small intestinal ulcer, large intestinal ulcer, anal ulcer)* (see section 4.4), vomiting, nausea	Gastrointestinal perforation*, fistula (anal, genital, gastrointestinal and skin fistula)* (see section 4.4)			
Hepatobiliary disorders					Liver disorders such as hepatitis, cholestasis, or jaundice	
Skin and subcutaneous tissue disorders		Skin and mucosal ulcerations (mainly peri-anal ulcerations, genital ulcerations and parastomal ulcerations) (see section 4.4)		Rash, pruritus	Angioedema	
Musculoskeletal and connective tissue disorders				Myalgia		

General disorders and administration site conditions		Feeling of weakness				

*The frequencies were calculated on the basis of the results of the Post Authorisation Safety Study (PASS), which is a retrospective cohort study which was conducted using the UK Clinical Practice Research Datalink (CPRD) database. Therefore, the frequencies represent those of the UK population.

Description of selected adverse reactions

Gastrointestinal ulcerations

Complications of gastrointestinal ulceration such as perforation, fistula, or abscess formation sometimes leading to gastrointestinal haemorrhage and weight loss have been reported (see section 4.4).

Additional information

In addition, the following adverse reactions have been reported with different frequencies in the IONA (Impact of Nicorandil in Angina) study, where nicorandil has been used on top of standard therapy in patients with stable angina and at high risk of cardiovascular events (see section 5.1).

	Common	**Uncommon**	**Very rare**
Gastrointestinal disorders	Rectal bleeding	Mouth ulcer	Abdominal pain
Skin and subcutaneous tissue disorders		Angioedema	
Musculoskeletal & connective tissue disorders		Myalgia	

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:
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms
In case of acute overdose, the likely symptomatology may be peripheral vasodilation with a fall in blood pressure and reflex tachycardia.

Management
Monitoring cardiac function and general supportive measures are recommended. If not successful, increase in circulating plasma volume by s fluid substitution is recommended. In life-threatening situations, administration of vasopressors must be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other vasodilators used in cardiac diseases, ATC code: C01DX16

Mechanism of action

Nicorandil, a nicotinamide ester, is a vasodilator agent with a dual mechanism of action, which leads to relaxation of smooth tonic vascular muscles in both venous and arterial part of vessels.

It possesses a potassium channel opening effect. This activation of potassium channels induces vascular cell membrane hyperpolarisation with an arterial muscle relaxant effect, thereby leading to arterial dilation and afterload reduction. In addition, the activation of the potassium channel leads to cardioprotective effects mimicking ischemic preconditioning.

Due to its nitrate moiety, nicorandil also relaxes vascular smooth muscle, particularly in the venous system via an increase in intracellular cyclic guanosine monophosphate (cGMP). This results in an increased pooling in capacitance vessels with a decrease in preload.

Pharmacodynamic effects

Nicorandil has been shown to exert a direct effect on coronary arteries, both on normal and stenotic segments, without leading to a steal phenomenon. Furthermore, the reduction of end-diastolic pressure and wall tension decreases the extravascular component of vascular resistance. Ultimately, this results in an improved oxygen balance in the myocardium and improved blood flow in the post-stenotic areas of the myocardium.

Furthermore, nicorandil has demonstrated a spasmolytic activity in both *in vitro* and *in vivo* studies and reverses coronary spasm induced by methacholine or noradrenalin.

Nicorandil has no direct effect on myocardial contractility.

Clinical efficacy and safety

The IONA study was a randomised, double blind, placebo controlled study carried out in 5126 patients more than 45 years old with chronic stable angina, treated with standard anti-anginal therapies and at high risk of cardiovascular events defined by either: 1) previous myocardial infarction, or 2) coronary artery bypass grafting , or 3) coronary artery disease confirmed by angiography, or a positive exercise test in the previous two years, together with one of the following: left ventricular hypertrophy on the ECG, left ventricular ejection fraction ≤ 45%, or an end diastolic dimension of > 55 mm, age ≥ 65, diabetes, hypertension, peripheral vascular disease, or cerebrovascular disease. Patients were excluded from the study if they were receiving a sulphonylurea as it was felt these patients may not benefit; (sulphonylurea agents have the potential to close potassium channels and may thus antagonise some of the effects of nicorandil). Study follow up for endpoint analysis was between 12 and 36 months with a mean of 1.6 years.

The composite primary endpoint [coronary heart disease (CHD) death, non-fatal myocardial infarction, or unplanned hospital admission for cardiac chest pain], occurred in 337 patients (13.1%) treated with nicorandil 20 mg twice daily compared with 389 patients (15.5%) receiving placebo [hazard ratio 0.83; 95% confidence interval (CI) 0.72 to 0.97; p=0.014].

5.2 Pharmacokinetic properties

Nicorandil pharmacokinetics are linear from 5 mg to 40 mg.

Absorption

After oral administration, nicorandil is absorbed rapidly and completely from the gastrointestinal tract, independent from food intake. The absolute bioavailability is about 75%. There is no significant hepatic first pass effect. Maximum plasma concentrations (C_{max}) are reached after about 30 to 60 minutes. The plasma concentration [and the area under the curve (AUC)] shows a linear proportionality to the dose.

Steady state is rapidly achieved (within 4 to 5 days) during repeated oral administration (bid regimen). At steady state, the accumulation ration (based on AUC) is around 2 for 20 mg bid tablet and 1.7 for 10 mg bid tablet.

Distribution

Distribution of the product throughout the body remains stable, irrespective of dose, within the therapeutic range.

The volume of distribution of nicorandil after intravenous (iv) dosing is 1.04 L/kg of body weight. Nicorandil is only slightly bound to human plasma proteins (bound fraction estimated at about 25%).

Biotransformation

Nicorandil is principally metabolised in the liver by denitration into a series of compounds without cardiovascular activity. In plasma unchanged nicorandil accounted for 45.5% of the radioactive AUC and the alcohol metabolite, N-(20hydroxyethyl)-nicotinamide for 40.5%. The other metabolites accounted for the remaining 20% of the radioactive AUC.

Nicorandil is mainly eliminated in urine as metabolites since parent product is less than 1% of the administered dose in human urine (0 – 48 hours). N-(2-hydroxyethyl)-nicotinamide is the most abundant metabolite (about 8.9% of the administered dose within 48 hours) followed by nicotinuric acid (5.7%), nicotinamide (1.34%), N-methyl-nicotinamide (0.61%) and nicotinic acid (0.40%). These metabolites represent the major route of transformation of nicorandil.

Elimination

Decrease in plasma concentrations occurs in two phases:

- the main phase of elimination has a half-life of about 2 hours;
- a slow elimination phase occurring approximately 12 hours following 20 mg oral dose bid.

After 4 – 5 mg intravenous dosing (5 min infusion), the total body clearance was approximately 40 - 55 L/hour.

Nicorandil and its metabolites are mainly excreted by urinary route, faecal excretion being very low.

Special patient groups

No clinically relevant modifications of the nicorandil pharmacokinetic profile is evidenced in population at risk such as elderly people, liver disease patients and chronic renal failure patients.

Pharmacokinetic interactions

The metabolism of nicorandil appears not to be significantly modified by cimetidine or rifampicin, respectively an inhibitor and an inducer of liver microsomal mixed-function oxidases.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Impairment of fertility
Fertility studies showed no effects on mating ability in either male or female rats, decreases in the number of live foetuses and implantation sites were noted at high doses. Histopathological changes of the testes (diminished spermatogenic cells) were determined in repeated dose toxicity studies. Additional investigative studies for testicular toxicity revealed decreased blood flow in the testis and decreased blood levels of testosterone. These results suggest that testicular toxicity by nicorandil is related to a sustained decrease in blood flow caused by reduction of cardiac output. Upon cessation of treatment, recovery from nicorandil-induced testicular toxicity was observed after 4 weeks; which indicates that the observed changes are reversible.

Embryotoxicity and peri and post-natal toxicity
Radioactivity passed through the placenta in pregnant rats after administration of radioactively marked nicorandil.

Following exposure to nicorandil at doses that were maternally toxic, embryotoxicity was observed in the rat and rabbit. There was no evidence of teratogenicity (rat and rabbit), or abnormal pre- or post-natal physical or behavioural development (rat).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Cetyl alcohol
Croscarmellose sodium
Povidone
Sodium stearyl fumarate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months

6.4 Special precautions for storage

Store below 25^{o}C. Store in the original package to protect from moisture.

6.5 Nature and contents of container

Nicorandil 10mg Tablets are packed in Alu /Alu blisters with an integrated desiccant layer.

The blister strips are packaged in cartons of 10, 28, 30, 56 and 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Dexcel Pharma GmbH
Carl-Zeiss-Strasse 2
63755 Alzenau
Germany

8 MARKETING AUTHORISATION NUMBER

PA2261/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 5th August 2011

Date of Last Renewal: 27th June 2016

10 DATE OF REVISION OF THE TEXT

August 2021