SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nicoril 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of nicorandil.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Tablets are white, round, scored on one side and embossed on the other side with '10'.
The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nicoril is 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

Nicoril is not recommended in paediatric patients since its safety and efficacy have not been established in this patient group.

Method of administration
Nicoril is administered by oral route.
The tablets are to be swallowed in the morning and in the evening as a whole with some liquid. Administration is independent from 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 ulcerations 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 permanently 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 Steroid 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 of corticosteroids 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 section 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 very rarely reported 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).

Desiccant
The tablets are sensitive to moisture; hence the patients should be advised to keep the tablets in their blister until intake. Besides the nicorandil tablets, in each blister each tablet is linked to a molecular sieve desiccant in a separate blister segment which is marked accordingly. The patients should be advised not to take these tablets. Although any accidental intake of this desiccant is usually harmless, it may alter the scheduled intake of the active tablets.

Paediatric population
Nicorandil is not recommended in paediatric patients since its safety and efficacy have not been established in this patient group.

G6PD deficiency
Nicorandil should be used with caution in patients with glucose-6-phosphate-dehydrogenase deficiency. Nicorandil acts in parts through its organic nitrate moiety. The metabolism of organic nitrates can result in the formation of nitrites which may trigger methemoglobinemia in patients with glucose-6-phosphate dehydrogenase deficiency.

4.5 Interaction with other medicinal products and other forms of interaction

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 (synergic effect).
Concomitant use of soluble guanylate cyclase stimulator (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 perforation in the context of concomitant use of nicorandil and corticosteroids has been reported. Caution is advised when concomitant use is considered.

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 Ferility, 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 Nicoril 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 Nicoril is 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

Nicoril has 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 the 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 of 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, <1/10), Uncommon (≥1/1,000, <1/100), Rare (≥1/10,000, <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 section 4.4 and 4.5)	
Nervous system disorders	Headache	Dizziness				IIIrd nerve paralysis, VIth nerve

						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 ulcers	abdominal pain
Skin and subcutaneous tissue disorders		Angioedema	

Musculoskeletal and 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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard.

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 of cardiac function and general supportive measures are recommended. If not successful, increase in circulating plasma volume by substitution of fluid 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 dilatation and afterload reduction. In addition, the activation of the potassium channel leads to cardioprotective effects mimicking ischemic pre-conditioning.

Due to its nitrate moiety, nicorandil relaxes also 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 the 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 antianginal 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 $\leq$ 45%, or an end diastolic dimension of > 55 mm, age $\geq$ 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 30-60 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 ratio (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 in a series of compounds without cardiovascular activity. In plasma unchanged nicorandil accounted for 45.5% of the radioactive AUC and the alcohol metabolite, N-(2-

hydroxyethyl)-nicotinamide for 40.5%. The other metabolites accounted for the remaining 20% of radioactive AUC.
Nicorandil is mainly eliminated in urine as metabolites since parent product is less than 1%, of the administered dose in human urines (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 represented the major route of transformation of nicorandil.

Elimination
Decrease in plasma concentrations occurs in two phases:

- a rapid phase with a half-life of 1 hour approximately, representing 96% of the plasma exposure;
- 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 rifampicine, 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, but decreases in the number of live fetuses and implantation sites were noted at high doses. Histopathological changes of the testes (diminished spermatogenic cells) were determined in repeat 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

Maize starch

croscarmellose sodium

stearic acid

mannitol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

Each blister should be used within 30 days of opening.

6.4 Special precautions for storage

Store below 25°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Alu/Alu blister of 10 tablets. In each blister each tablet is linked to a molecular sieve desiccant. The blisters are packed in cartons of 20 and 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Rivopharm UK Ltd.

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London

EC2N 4AG

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 33155/0023

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/01/2011

10 DATE OF REVISION OF THE TEXT

30/08/2023