

Nicorandil 10mg Tablets

Nicorandil 20mg Tablets

PL 33155/0001

PL 33155/0003

UKPAR

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NICORANDIL 10MG TABLETS

NICORANDIL 20MG TABLETS

PL 33155/0001

PL 33155/0003

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) for the medicinal products Nicorandil 10mg and 20mg Tablets (Product Licence numbers: PL 33155/0001 and PL 33155/0003) on 18 November 2010.

Nicorandil is used to help relieve angina. Angina is chest pain that occurs when the heart muscle does not receive enough blood to supply it with oxygen when it is working hard. Angina can be brought on by physical activity, sudden cold or stress. Nicorandil relieves angina by widening the blood vessels that supply the heart muscle to increase the blood supply. Nicorandil also opens up blood vessels elsewhere in the body to reduce the amount of work the heart has to do to pump blood around the body.

Nicorandil 10mg and 20mg Tablets raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.

NICORANDIL 10MG TABLETS

NICORANDIL 20MG TABLETS

PL 33155/0001

PL 33155/0003

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products Nicorandil 10mg and 20mg Tablets to Rivopharm UK Limited on 18 November 2010. These medicines are only available on prescription.

Nicorandil 10mg and 20mg Tablets are used in the prevention and long term treatment of chronic stable angina pectoris. More specifically, they reduce the risk of acute coronary syndromes in patients with chronic stable angina and at least one of the following risk factors:

- Previous MI
- Previous CABG
- CHD on angiography or a positive exercise test together with one of the following: LVH on ECG, left ventricular dysfunction, age $\geq$ 65, diabetes mellitus (type I or II, excluding those on sulphonylureas), hypertension or documented vascular disease.

These applications are submitted under Article 10(1) of Directive 2001/83/EC, as amended. The applicant claims that Nicorandil 10mg and 20mg Tablets are generic versions of Ikorel 10mg and 20mg tablets, respectively. Ikorel tablets have been authorised in France since 12 August 1992, the legal basis of these applications is, therefore, acceptable and the ten year rule is complied with.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE: NICORANDIL

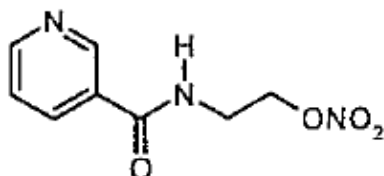
General Information

Nomenclature

INN: Nicorandil

Chemical names: *N*-[2-(Nitro-oxy)ethyl]-3-pyridine carboxamide

Structure



Molecular formula: C₈H₉N₃O₄

Molecular mass: 211.18 g/mol

General properties

A white to light cream, crystalline powder with a melting point of 87-93 °C. It is slightly soluble in water, methanol and ethanol.

Manufacture

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Control

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Container closure system

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Stability

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

Drug Product

Nicorandil 10mg and 20mg Tablets contain the pharmaceutical excipients maize starch, croscarmellose sodium, stearic acid and mannitol.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory certificates of analysis have been provided for all excipients.

Pharmaceutical development

The objective of the development programme was to formulate robust, stable tablets that contain qualitatively and quantitatively the same active ingredient as Ikorel 10mg and 20mg tablets and exhibit the same bioavailability in order to comply with the regulations pertaining to generic medicinal product applications.

Suitable pharmaceutical development data have been provided for these applications. The physico-chemical properties of the drug product have been compared with those of the originator product. These data demonstrate that the proposed products can be considered generic versions of Ikorel tablets 10mg and 20mg tablets.

Manufacture

A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory, based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results are satisfactory.

Finished product specification

The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for any working standards used.

Container closure system

The finished products are packed in Alu/Alu blister strips of 10 tablets. In each blister each tablet is linked to a molecular sieve desiccant. The blister strips are packed in cartons of 60 tablets.

Specifications and certificates of analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 18 months has been set for the products when stored in a closed container, with a shelf-life of 30 days after first opening the blister strip. The special precautions for storage are “Do not store above 25 C” and “Store in the original package in order to protect from moisture”.

Bioequivalence/bioavailability

Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study. Bio-analytical methods used have been satisfactorily validated. Bioequivalence has been demonstrated between the test and reference products.

Expert report

A satisfactory expert report is provided from an appropriately qualified author.

Product literature

The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Pharmaceutical Conclusion

It is recommended that Marketing Authorisations are granted for these applications.

PRECLINICAL ASSESSMENT

As the pharmacodynamic, pharmacokinetic and toxicological properties of nicorandil are well-known, no further preclinical studies are required and none have been provided.

The applicant's preclinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of these products from a preclinical viewpoint.

CLINICAL ASSESSMENT

Pharmacokinetics

A single bioequivalence study has been submitted. This was a randomised, open-label, 2-way crossover, bioequivalence study of Nicorandil 10mg Tablets and Ikorel (reference) following a 10 mg dose in healthy subjects under fasting conditions. The applicant has provided assurance that the study complied with GCP and GLP requirements.

A total of 36 subjects (16 females and 20 males) were enrolled and randomised, three dropped out, and one withdrew. In all, 32 subjects completed the study. The washout period was 7 days and the sampling period was up to 10 hours post dose. The test product was Nicorandil 10mg Tablets and the reference product was Ikorel 10mg tablet.

SUMMARY OF RESULTS: NICORANDIL (*n* = 32)

Pharmacokinetic parameters

Parameters	Test (Nicorandil (A))			Reference (Ikorel (B))		
	Mean (%)	SD	CV	Mean (%)	SD	CV
AUC _{0-t} (ng.h/mL)	41.26	56.90	23.58	254.15	52.87	20.80
AUC _{0-inf} (ng.h/mL)	242.77	56.88	23.43	255.74	52.46	20.51
C _{max} (ng/mL)	173.59	47.09	27.13	201.01	79.99	39.79
T _{max} (h)	0.448	0.237	52.95	0.396	0.238	60.18
T _{½ el} (h)	1.51	0.51	33.59	1.44	0.55	38.49

Nicorandil (A) vs Ikorel (B)

	AUC _{0-t}	AUC _{0-inf}	C _{max}
Ratio ¹	94.50%	94.48%	89.76%
90% geometric C.I. ²	89.15% to 100.18%	89.19% to 100.08%	80.17% to 100.48%
Intra-subject CV	13.78 %	13.61 %	27.03 %

¹ Calculated using least-squares means according to the formula: $e^{\frac{\ln(\text{Nicorandil (A)} - \text{Ikorel (B)})}{n}} \times 100$

² 90% Geometric confidence interval using In-transformed data

The study design is acceptable and the reference product chosen was appropriate. The washout period and the sampling period were adequate.

The study results demonstrate bioequivalence between the test and reference products.

Efficacy

No new data on the efficacy of these products have been submitted and none are required for these types of applications.

Safety

No new or unexpected safety issues were raised by the bioequivalence study.

Product literature

The SPCs, PILs and labels are medically acceptable. The SPCs are consistent with those for the originator products.

Pharmacovigilance System

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The applicant has not submitted an RMP, nor is one needed for an application of this kind.

Clinical Expert Report

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion

The grant of Marketing Authorisations is recommended.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Nicorandil 10mg and 20mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the risk-benefit balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

The efficacy of nicorandil is well established. Bioequivalence has been demonstrated between the applicant's product and the reference product.

SAFETY

No new or unexpected safety concerns arise from these applications.

The SPCs, PILs and labelling are satisfactory and consistent with those for the reference product.

RISK-BENEFIT ASSESSMENT

The quality of the products is acceptable, and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the originator products are interchangeable. Extensive clinical experience with nicorandil is considered to have demonstrated the therapeutic value of the compound. The risk benefit ratio is, therefore, considered to be acceptable for these products and Marketing Authorisations may be granted.

NICORANDIL 10MG TABLETS

NICORANDIL 20MG TABLETS

PL 33155/0001

PL 33155/0003

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the Marketing Authorisation applications on 12 June 2008
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 18 June 2008
3	Following assessment of the applications the MHRA requested further information relating to the quality dossier on 15 August 2008 and the clinical dossier on 5 September 2008
4	The applicant responded to the MHRA's requests, providing further information on the quality and clinical dossiers on 9 February 2009
5	Following assessment of the response the MHRA requested further information relating to the quality dossier on 21 May 2009 and the clinical dossier on 5 June 2009
6	The applicant responded to the MHRA's requests, providing further information on the quality and clinical dossiers on 18 March 2010
7	Following assessment of the response the MHRA requested further information relating to the quality dossier on 14 July 2010
8	The applicant responded to the MHRA's request, providing further information on the quality dossier on 13 August 2010
9	The applications were determined on 18 November 2010

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nicorandil 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg of nicorandil.

For a full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Tablet

White, round, scored on one side and embossed on the other side with '10'.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Prevention and long term treatment of chronic stable angina pectoris
- Reduction in the risk of acute coronary syndromes in patients with chronic stable angina and at least one of the following risk factors:
 - Previous MI
 - Previous CABG
 - CHD on angiography **or** a positive exercise test together with one of the following: LVH on ECG, left ventricular dysfunction, Age ≥ 65 , diabetes mellitus (type I or II excluding those on sulphonylureas, see section 5.1), hypertension or documented vascular disease

4.2 Posology and method of administration

Adults: The recommended starting dose is 10mg nicorandil twice daily, although 5mg twice daily may be employed in patients particularly susceptible to headache.

Subsequently the dosage should be titrated upward depending on the clinical response. The usual therapeutic dosage is in the range 10 to 20mg nicorandil twice daily, although up to 30mg daily may be employed if necessary.

Elderly: There is no special requirement for dosage reduction in elderly patients. As with all medicines, the lowest effective dosage should be used.

Children: A paediatric dosage has not been established and use of nicorandil is not recommended.

Route of administration: oral

4.3 Contraindications

Nicorandil is contraindicated in patients with cardiogenic shock, left ventricular failure with low filling pressures and in hypotension. It is also contraindicated in patients who have demonstrated an idiosyncratic response or hypersensitivity to nicorandil. Due to the risk of severe hypotension, the

concomitant use of Nicorandil and phosphodiesterase 5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) is contraindicated.

4.4 Special warnings and precautions for use

The use of nicorandil should be avoided in patients with depleted blood volume, low systolic blood pressure, acute pulmonary oedema or acute myocardial infarction with acute left ventricular failure and low filling pressures.

Therapeutic doses of nicorandil may lower the blood pressure of hypertensive patients and therefore nicorandil, as with other antianginal agents, should be used with care when prescribed with antihypertensive drugs.

Alternative therapy should be considered if persistent aphtosis or severe mouth ulceration occurs.

4.5 Interaction with other medicinal products and other forms of interaction

No pharmacological or pharmacokinetic interactions have been observed in humans or animals with beta-blockers, digoxin, rifampicin, cimetidine, acenocoumarol, a calcium antagonist or a combination of digoxin and furosemide. Nevertheless, there is the possibility that nicorandil may potentiate the hypotensive effects of other vasodilators, tricyclic antidepressants or alcohol.

As the hypotensive effects of nitrates or nitric oxide donors are potentiated by phosphodiesterase 5 inhibitors, the concomitant use of Nicorandil Rivopharm and phosphodiesterase 5 inhibitors is contraindicated.

4.6 Pregnancy and lactation

Pregnancy: Animal studies have not revealed any harmful effect of nicorandil on the foetus although there is no experience in humans. It should not be used in pregnant patients unless there is no safer alternative.

Lactation: As it is not known whether nicorandil is excreted in human milk, breastfeeding should be avoided by lactating patients who require therapy.

4.7 Effects on ability to drive and use machines

Patients should be warned not to drive or operate machinery until it is established that their performance is unimpaired by nicorandil.

4.8 Undesirable effects

The following undesirable effects have been reported from the original clinical trials for the prevention and long-term treatment of chronic stable angina and post-marketing experience.

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), including isolated reports.

Immune system disorders

Very rare – Angioedema.

Nervous system disorders

Very common – Headache, usually of a transitory nature, especially when treatment is initiated.

Common – Dizziness

Cardiac disorders

Uncommon – An increase in heart rate at high doses.

Gastrointestinal disorders

Common – Nausea and vomiting

Rare – Persistent aphthosis or mouth ulcers which were occasionally severe

Very rare – Gastrointestinal ulcerations including anal ulcerations and rectal bleeding.

Potential complications may include fistulating disease.

Hepato-biliary disorders

Rare – Hepatic function abnormalities.

Skin and subcutaneous tissue disorders

Rare – Various types of rash

Vascular disorders

Common – Cutaneous vasodilation with flushing.

Uncommon – Hypotension at high therapeutic doses.

Musculoskeletal & connective tissue disorders

Rare – Myalgia

General disorders and administration site conditions

Common – A feeling of weakness

Other Clinical Trials – IONA (Impact of Nicorandil in Angina).

In addition, the following undesirable effects occurred at a different frequency in the IONA trial which was a study of subjects at high risk of cardiovascular events.

Gastrointestinal disorders

Common – rectal bleeding.

Uncommon – Cases of gastritis and oesophagitis were noted in the IONA study, but the difference in incidence between the nicorandil group and the placebo group was not statistically significant.

Uncommon – mouth ulcers

Very Rare – abdominal pain

The clinical expression of diverticular disease may possibly be increased with nicorandil[1]

[1] A statistically significant difference ($p=0.039$) has been found between the nicorandil (20 cases = events) and the placebo group (5 cases = events) in the IONA study, with enrolment of 5126 patients.

Immune system disorders

Uncommon – angioedema

Musculoskeletal & connective tissue disorders

Uncommon – myalgia

4.9 Overdose

Acute overdosage is likely to be associated with peripheral vasodilation, decreased blood pressure and reflex tachycardia. Cardiac function should be monitored and general supportive measures employed. If necessary, circulating plasma volume should be increased by infusion of suitable fluid. In life-threatening situations, administration of vasopressors should be considered. There is not experience of massive overdosage in humans, although the LD₅₀ in dogs is in the range 62.5 to 125 mg/kg and in rodents it is in the order of 1200 mg/kg.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other vasodilators used in cardiac diseases

ATC code: C01DX16

Nicorandil provides a dual mode of action leading to relaxation of vascular smooth muscle. A potassium channel opening action provides arterial vasodilation, thus reducing afterload, while the nitrate component promotes venous relaxation and reduction in preload. Nicorandil has a direct effect on coronary arteries without leading to a steal phenomenon. The overall action improves blood flow to post-stenotic regions and the oxygen balance in the myocardium.

A reduction of coronary heart disease complications has been shown in patients suffering from angina pectoris who were treated with nicorandil in the IONA study.

The study was a randomised, double blind, placebo controlled, cardiovascular endpoint study carried out in 5126 patients to determine if Nicorandil could reduce the frequency of coronary events in men and women with chronic stable angina and standard anti anginal treatment 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 ≤ 65 , diabetes (either type 1 or type 2), 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 primary endpoint of coronary heart disease (CHD) death, non-fatal myocardial infarction, or unplanned hospital admission for cardiac chest pain, occurred in 13.1% of patients treated with nicorandil compared with 15.5% of patients receiving placebo (hazard ratio 0.83, $p=0.014$). The rate of acute coronary syndrome (CHD death, non fatal MI or unstable angina) was 6.1% in patients treated with nicorandil compared with 7.6% in patients receiving placebo (hazard ratio 0.79, $p=0.028$). All cardiovascular events were significantly less in the nicorandil than placebo group 14.7% vs 17.0% (hazard ratio 0.86, $p=0.027$). The validity of these findings was confirmed by re-analysing the primary endpoint using all cause rather than cardiovascular mortality (nicorandil 14.9% compared with placebo 17.3%, hazard ratio 0.85, $p=0.021$). The study was not expressly powered to, nor did it detect any statistically significant reduction in any individual component endpoints.

5.2 Pharmacokinetic properties

Nicorandil is well absorbed with no significant first-pass metabolism. Maximum plasma concentrations are achieved in 30 to 60 minutes and are directly related to the dosage. Metabolism is mainly by denitration of the molecule into the nicotinamide pathway with less than 20% of an administered dose being excreted in the urine. The main phase of elimination has a half-life of about 1 hour. Nicorandil is only slightly bound to plasma proteins.

No clinically relevant modifications in the pharmacokinetic profile have been seen in the elderly or in patients with liver disease or chronic renal failure.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
croscarmellose sodium
stearic acid
mannitol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

Each blister strip should be used within 30 days of opening.

- 6.4 Special precautions for storage**
Do not store above 25°C. Store in the original package in order to protect from moisture.
- 6.5 Nature and contents of container**
Alu/Alu blister strips of 10 tablets. In each blister each tablet is linked to a molecular sieve desiccant. The blisters strips are packed in cartons of 60 tablets.
- 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 Limited, 6th floor, 28 Kingsway, London WC2B 6JR - UK
- 8 MARKETING AUTHORISATION NUMBER(S)**
PL 33155/0001
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
18/11/2010
- 10 DATE OF REVISION OF THE TEXT**
18/11/2010
- 1 NAME OF THE MEDICINAL PRODUCT**
Nicorandil 20mg Tablets
- 2 QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each tablet contains 20mg of nicorandil.

For a full list of excipients see Section 6.1
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Nicorandil provides a dual mode of action leading to relaxation of vascular smooth muscle. A potassium channel opening action provides arterial vasodilation, thus reducing afterload, while the nitrate component promotes venous relaxation and reduction in preload. Nicorandil has a direct effect on coronary arteries without leading to a steal phenomenon. The overall action improves blood flow to post-stenotic regions and the oxygen balance in the myocardium.

A reduction of coronary heart disease complications has been shown in patients suffering from angina pectoris who were treated with nicorandil in the IONA study.

The study was a randomised, double blind, placebo controlled, cardiovascular endpoint study carried out in 5126 patients to determine if Nicorandil could reduce the frequency of coronary events in men and women with chronic stable angina and standard anti anginal treatment 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 ≤ 65 , diabetes (either type 1 or type 2), 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 primary endpoint of coronary heart disease (CHD) death, non-fatal myocardial infarction, or unplanned hospital admission for cardiac chest pain, occurred in 13.1% of patients treated with nicorandil compared with 15.5% of patients receiving placebo (hazard ratio 0.83, $p=0.014$). The rate of acute coronary syndrome (CHD death, non fatal MI or unstable angina) was 6.1% in patients treated with nicorandil compared with 7.6% in patients receiving placebo (hazard ratio 0.79, $p=0.028$). All cardiovascular events were significantly less in the nicorandil than placebo group 14.7% vs 17.0% (hazard ratio 0.86, $p=0.027$). The validity of these findings was confirmed by re-analysing the primary endpoint using all cause rather than cardiovascular mortality (nicorandil 14.9% compared with placebo 17.3%, hazard ratio 0.85, $p=0.021$). The study was not expressly powered to, nor did it detect any statistically significant reduction in any individual component endpoints.

5.2 Pharmacokinetic properties

Nicorandil is well absorbed with no significant first-pass metabolism. Maximum plasma concentrations are achieved in 30 to 60 minutes and are directly related to the dosage. Metabolism is mainly by denitration of the molecule into the nicotinamide pathway with less than 20% of an administered dose being excreted in the urine. The main phase of elimination has a half-life of about 1 hour. Nicorandil is only slightly bound to plasma proteins. No clinically relevant modifications in the pharmacokinetic profile have been seen in the elderly or in patients with liver disease or chronic renal failure.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
croscarmellose sodium
stearic acid
mannitol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

Each blister strip should be used within 30 days of opening.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

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

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 Limited, 6th floor, 28 Kingsway, London WC2B 6JR - UK

- 8 MARKETING AUTHORISATION NUMBER(S)**
PL 33155/0003
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**
18/11/2010
- 10 DATE OF REVISION OF THE TEXT**
18/11/2010

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Nicorandil 10mg Tablets Nicorandil 20mg Tablets

Nicorandil

Read all of this leaflet carefully before you start taking this medicine.

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

In this leaflet:

1. What Nicorandil is and what it is used for
2. Before you take Nicorandil
3. How to take Nicorandil
4. Possible side effects
5. How to store Nicorandil
6. Further information

1. WHAT NICORANDIL IS AND WHAT IT IS USED FOR

Nicorandil belongs to a group of medicines called potassium channel activators.

Your doctor has prescribed Nicorandil to help relieve your angina.

Angina is a chest pain that occurs when the heart muscle does not receive enough blood to supply it with oxygen when it is working hard. Angina can be brought on by physical activity, sudden cold or stress.

Nicorandil relieves angina by widening the blood vessels that supply the heart muscle to increase the blood supply. Nicorandil also opens up blood vessels elsewhere in the body to reduce the amount of work the heart has to do to pump blood around the body.

2. BEFORE YOU TAKE NICORANDIL

Do not take Nicorandil:

- if you are allergic (hypersensitive) to nicorandil or any of the other ingredients in this medicine. (See section 6 of this leaflet for a list of ingredients)

Signs of allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.

- if you have any heart conditions such as a low blood output from the heart or if you have suffered from heart failure

- if you have low blood pressure

- if you are using medicines for treating impotence such as sildenafil, tadalafil and vardenafil.

Take special care with Nicorandil

Tell your doctor before you take Nicorandil if you:

- have severe mouth ulcerations
- are taking medicines to treat high blood pressure.

Children and adolescents under the age of 18 years:

Nicorandil is not recommended for use in children and adolescents under the age of 18 years.

Taking/using other medicines:

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Nicorandil can affect the way some other medicines work and some medicines can affect the way nicorandil works.

Please tell your doctor if you are taking or have recently taken:

- medicines for blood pressure or angina that work on blood vessels such as hydralazine and minoxidil
- antidepressants such as amitriptyline, doxepin and imipramine
- alcohol
- medicines used to treat impotence such as sildenafil, tadalafil and vardenafil.

Taking Nicorandil with food and drink:

Do not drink alcohol while you are taking this medicine.

Pregnancy and breast-feeding:

Ask your doctor or pharmacist for advice before taking any medicine.

If you are pregnant or think you might be pregnant you should not use Nicorandil.

If you are breast-feeding you should not use Nicorandil.

Driving and using machines:

You may feel dizzy while you are using this medicine. If you are affected do not drive or use machinery.

3. HOW TO TAKE NICORANDIL

Always take Nicorandil exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. You should continue to take your Nicorandil for as long as your doctor tells you to.

Tablets should be swallowed whole or halved with a glass of water at the same time each day.

Adults and the elderly:

Your doctor will usually start your treatment with a dose of 10mg twice daily, to be taken in the morning and evening. Your doctor may increase this dose if necessary. The usual maximum dose is 30mg twice daily.

If you have a tendency to get headaches, your doctor may start you on a lower dose of 5mg (half a 10mg tablet) twice a day.

The same doses can be used in patients that are older than 70 years of age.

If you take more Nicorandil than you should:

If you take more Nicorandil tablets than you should, contact your doctor or the nearest hospital emergency department. Symptoms of overdose are you may feel dizzy or weak or have difficulty breathing or experience wheezing.

If you forget to take a Nicorandil:

Do not worry if you have missed a dose. Take your next dose at the right time and then carry on as before. Do not take a double dose next time to make up for a forgotten dose.

If you stop taking Nicorandil:

As the treatment for angina is usually life-long, you should discuss with your doctor before stopping this medicinal product.

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

4. POSSIBLE SIDE EFFECTS

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

If you experience the following, stop taking this medicine and tell your doctor immediately or go to the casualty department of your nearest hospital:

- A severe allergic reaction (rash, itching, swelling of the face, lips, mouth or throat that may cause difficulty in swallowing or breathing).

This is a serious but very rare side effect, which affects less than 1 patient out of 10,000 patients. You may need urgent medical attention or hospitalisation.

The following side effects may also occur:

Very Common (affecting more than 1 in every 10 people)

- Headaches - these may occur in the first few days of treatment, but should disappear with time. If not, talk to your doctor

Common (affecting up to 1 in 10 people)

- Feeling sick or vomiting
- Weakness or dizziness
- Flushing

Uncommon (affecting more than 1 in 1,000 patients but less than 1 in 100 patients)

- An increase in heart rate when taking high doses
- Low blood pressure when taking high doses

Rare (affecting more than 1 in 10,000 patients but less than 1 in 1,000)

- Muscle pain
- Rashes
- Persistent mouth ulcers
- Liver function abnormalities detected by blood test.

Very Rare (affecting fewer than 1 in 10,000 patients)

- Swelling of the skin similar to hives
- Ulcers including ulcers and bleeding of the back passage

If you experience any of the following tell your doctor immediately:

- Palpitations - sensations of fast or irregular heartbeat
- Ulcers or pain of the back passage
- Bleeding or discharge of pus from the back passage or abnormal vaginal discharge
- Swelling, tenderness, irritation and itching on the skin around the back passage
- Vomiting blood, severe or lasting stomach pains or dark, tarry stools
- Swelling of the lips and tongue.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In a clinical study conducted in subjects at high risks of heart disease, the following side effects occurred:

Common (affecting up to 1 in 10 people)

- Bleeding from the back passage.

Uncommon (affecting more than 1 in 1,000 patients but less than 1 in 100 patients)

- Mouth ulcers
- Swelling of the skin similar to hives
- Muscle pain

Very rare (affecting fewer than 1 in 10,000 patients)

- Stomach pain

5. HOW TO STORE NICORANDIL

Keep out of the reach and sight of children.

Do not use Nicorandil after the expiry date which is stated on the outer carton and the blister foil. The expiry date refers to the last day of that month.

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

Do not swallow the drying agent which is contained in the strip.

Use the blister strip within 30 days of opening.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION**What Nicorandil contains:**

- The active substance is nicorandil. Two strengths of tablets are available. The strengths are 10mg and 20mg.
- Other ingredients are maize starch, croscarmellose sodium, stearic acid and mannitol (E421).

What Nicorandil looks like and contents of the pack:

Nicorandil 10 mg tablets are white, round, scored on one side and embossed with '10' on the other side. Nicorandil 20 mg tablets are white, round, scored on one side and embossed with '20' on the other side. Nicorandil 10 mg tablets and 20 mg tablets are available in blister packs. Each blister contains 10 tablets. The blisters are packed in cartons of 60 tablets.

Marketing Authorisation Holder and Manufacturer:**Marketing Authorisation Holder**

Rivopharm UK
6th floor 28 Kingsway, London WC2B 6JR, UK

Manufacturer

Laboratoires BTT
ZI de Krafft - 67150 ERSTEIN- France.

Distributed by:

Genus Pharmaceuticals
Park View House, 65 London Road,
Newbury, Berkshire RG14 1JN, UK.

This leaflet was approved in November 2010

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Nicorandil 10mg Tablets Nicorandil 20mg Tablets

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Pregnancy and breast-feeding:

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Rivopharm UK
6th floor 28 Kingsway, London WC2B 6JR, UK

Manufacturer

Laboratoires BTT
ZI de Krafft - 67150 ERSTEIN- France.

Distributed by:

Creo Pharma Ltd,
Felsted Business Centre, Felsted,
Essex, CM6 3LY, UK

This leaflet was approved in November 2010

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LABELLING

10 mg tablets

Label:



Carton:



Label:



Carton:



20 mg tablets

Label:



Carton:



Label:



Carton:

