

NICORANDIL 10MG AND 20MG TABLETS

PL 31623/0081-2

UKPAR

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NICORANDIL 10MG AND 20MG TABLETS

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LAY SUMMARY

On 19th July 2011, the MHRA granted Dexcel-Pharma Laboratories Limited Marketing Authorisations (licences) for Nicorandil 10mg and 20mg Tablets.

Nicorandil 10mg and 20mg Tablets contain the active ingredient, nicorandil. Nicorandil belongs to a group of medicines called potassium-channel activators.

Nicorandil 10mg and 20mg Tablets are used to prevent and treat long-term chest pain (angina). They work by increasing the blood flow through the blood vessels of the heart.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Nicorandil 10mg and 20mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.

NICORANDIL 10MG AND 20MG TABLETS

PL 31623/0081-2

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted Dexcel-Pharma Laboratories Limited Marketing Authorisations for the medicinal products Nicorandil 10mg and 20mg Tablets (PL 31623/0081-2) on 19th July 2011. Nicorandil 10mg and 20mg Tablets are prescription only medicines (POM) and are indicated for:

- The prevention and long term treatment of chronic stable angina pectoris
- A reduction in the risk of acute coronary syndromes in patients with chronic stable angina and other risk factors.

These applications for Nicorandil 10mg and 20mg Tablets are submitted under Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products to Ikorel 10mg and 20mg Tablets first authorised in the UK to May and Baker Limited on 6th June 1994 (PL 00012/0229-30). These licences then underwent a change of ownership to Aventis Pharma Limited on 24th February 2009 (PL 04425/0327-8).

The Marketing Authorisation Holder has committed to submitting a Change of Ownership to Dexcel Pharma Limited at the earliest opportunity. Hence, there are no Product Licence numbers or Marketing Authorisation Holder details on the SmPC, Patient Information leaflet (PIL) or the labelling at this time. The Marketing Authorisation Holder has provided an assurance that the product(s) will not be marketed until the Change of Ownership has been completed.

Nicorandil provides a dual mode of action leading to relaxation of vascular smooth muscle. A potassium channel opening action provides arterial vasodilatation, thus reducing after load, while the nitrate component promotes venous relaxation and a reduction in preload. Nicorandil has a direct effect on coronary arteries and is indicated for the treatment of chronic stable angina pectoris and risk reduction of acute coronary syndrome in this group of patients.

The pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH 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.

A satisfactory justification was provided for the absence of a Risk Management Plan.

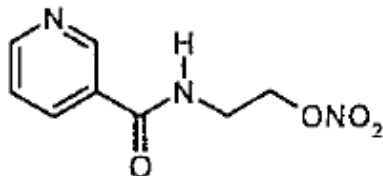
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

INN: Nicorandil

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

Structure:



Physical form: White to off-white crystalline powder

Solubility: Freely soluble in acetone, methanol, ethanol and acetonitrile; soluble in ethyl acetate and chloroform; sparingly soluble in water; and slightly soluble in ether

Molecular formula: C₈H₉N₃O₄

Molecular weight: 211.18 g/mol

Nicorandil complies with in-house specifications.

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 specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof of structure data has been supplied for the drug substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the drug substance, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all reference standards used.

Satisfactory specifications and Certificates of Analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate stability data have been generated showing the drug substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

DRUG PRODUCT

Other ingredients

Other ingredients are pharmaceutical excipients mannitol, cetyl alcohol, croscarmellose sodium, povidone, sodium stearyl fumarate and anhydrous colloidal silica.

All the ingredients comply with their relevant European Pharmacopoeia monographs.

None of the excipients used contain material of animal or human origin.

Product development

The objective of the development programme was to produce nicorandil containing products that could be considered generic medicinal products of Ikorel 10mg and 20mg Tablets.

A suitable product development section has been provided. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative *in vitro* impurity and dissolution profiles have been provided for the proposed and reference products.

Manufacture

A description and flow-chart of the manufacturing method has been provided. Satisfactory batch formulae have been provided for the manufacture of the products.

The manufacturing process has been validated and has shown satisfactory results.

In-process controls are satisfactory based on batch data and controls on the finished products.

Process validation data on batches of each strength have been provided and are satisfactory.

A commitment to perform process validation on commercial-scale batches of each strength has been provided.

Finished product specification

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

Container-Closure System

The tablets are packaged in aluminium blisters with an integrated desiccant layer. The strips are packed in cardboard cartons and come in pack sizes of 10, 28, 56 and 60 tablets.

Specifications and Certificates of Analysis have been provided. All primary product packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines.

Based on the results, a shelf life of 18 months has been set, with storage instructions 'Store below 25°C' and 'Store in original package to protect from moisture'. This is satisfactory.

ADMINISTRATIVE

Quality Overall Summary

A quality overall summary has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics (SmPCs)

These are satisfactory.

Labelling

These are satisfactory.

Patient Information Leaflet (PIL)

This is satisfactory.

User testing results have been submitted for the PIL for this product. The results indicate that the PIL 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.

MAA Forms

These are pharmaceutically satisfactory.

Conclusion

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

NON-CLINICAL ASSESSMENT

No new non-clinical data have been supplied with these applications and none are required for applications of this type.

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

A satisfactory justification was provided for the absence of an Environmental Risk Assessment.

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

To support the applications, the Marketing Authorisation Holder has included a single bioequivalence study:

A randomised, open-label, single dose, randomised, two-treatment, two-period, two-sequence, crossover bioequivalence study comparing the pharmacokinetics of Nicorandil 20mg Tablets (Test) versus Ikorel (Nicorandil) 20mg Tablets (Reference) in healthy volunteers under fasting conditions.

Blood sampling was performed pre-dose and up to 12 hours post dose in each treatment period. There was a washout period of 7 days. Pharmacokinetic parameters were calculated and statistically analysed.

Results from this study are presented below as log-transformed values: Geometric Least Mean Squares and 90% Confidence Interval

Pharmacokinetic parameters of nicorandil

Treatment	AUC _{0-t} (ng.h/mL)	AUC _{0-∞} (ng.h/mL)	C _{max} (ng/mL)
Test	500.87 ± 110.69	511.44 ± 110.46	484.71 ± 172.18
Reference	518.26 ± 108.61	526.75 ± 109.68	482.35 ± 208.86
Ratio (90% CI)	0.97 (0.92; 1.01)	0.97 (0.93; 1.02)	1.04 (0.89; 1.23)

AUC_{0-∞} area under the plasma concentration-time curve from time zero to infinity

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours

C_{max} maximum plasma concentration

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-t} and C_{max} for nicorandil lie within the normal 80-125% limits. Thus, bioequivalence has been shown between the test and reference products.

As the 10mg and 20mg tablet strengths meet all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 20mg strength can be extrapolated to Nicorandil 10mg Tablets.

EFFICACY

These are generic applications based on demonstration of bioequivalence and new data relating to efficacy are not required as per EU legislation once bioequivalence has been demonstrated.

SAFETY

These are generic applications based on demonstration of bioequivalence and new data relating to safety are not required as per EU legislation once bioequivalence has been demonstrated.

EXPERT REPORTS

The clinical expert report has been written by a suitably qualified person and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

This is consistent with that for the reference product and is satisfactory.

LABELLING

These are satisfactory.

APPLICATION FORMS (MAA)

These are satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPCs)

These are consistent with those for the reference products and are satisfactory.

DISCUSSION

The applicant has satisfactorily demonstrated bioequivalence between the test and reference products.

CLINICAL CONCLUSION

The bioequivalence study submitted, together with the additional data provided has shown that Nicorandil 10mg and 20mg Tablets can be considered as generic medicinal products to the reference products Ikorel 10mg and 20mg Tablets.

The grant of Marketing Authorisations is recommended for these applications.

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 benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Nicorandil 20mg Tablets and the reference product, Ikorel 20mg Tablets.

This conclusion can be extrapolated to Nicorandil 10mg Tablets.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

The Marketing Authorisation Holder has committed to submitting a Change of Ownership to Dexcel Pharma Limited at the earliest opportunity. Hence, there are no Product Licence numbers or Marketing Authorisation Holder details on the SmPC, Patient Information leaflet (PIL) or the labelling at this time. The Marketing Authorisation Holder has provided an assurance that the product(s) will not be marketed until the Change of Ownership has been completed.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the reference products are interchangeable. Clinical experience with nicorandil is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

NICORANDIL 10MG AND 20MG TABLETS**PL 31623/0081-2****STEPS TAKEN FOR ASSESSMENT**

1	The MHRA received the Marketing Authorisation Applications on 26 th October 2009.
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 10 th December 2009.
3	Following assessment of the application, the MHRA requested further information relating to the quality dossier on 25 th February 2010, 23 rd September 2010 and 23 rd March 2011. Further information relating to the clinical dossier was requested on 4 th February 2010.
4	The applicant responded to the MHRA's requests, providing further information on 31 st August 2010, 23 rd December 2010 and 8 th May 2011 for the quality section. Further information for the clinical section was provided on 30 th April 2010.
5	The applications were determined on 13 th July 2011. The application was completed on 19 th July 2011.

NICORANDIL 10MG AND 20MG TABLETS

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

Please note that there are no product licence numbers or Marketing Authorisation Holder details on the SmPC, PIL or labelling text below. The marketing authorisation holder has committed to submitting a change of ownership at the earliest opportunity and is therefore not intending to market the products until the Change of Ownership has been completed. A commitment has been provided to submit UK PIL and labelling for review to the regulatory authority before marketing the products.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nicorandil 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Nicorandil 10mg

Each tablet contains 10mg nicorandil.

For a 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 halves.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Nicorandil 10mg Tablets are indicated for the following:

- The prevention and long term treatment of chronic stable angina pectoris
- A 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

Route of administration: oral.

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 twice daily may be employed if necessary.

Elderly: For elderly patients use of the lowest effective dose is recommended.

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

4.3 CONTRAINDICATIONS

Nicorandil 10mg Tablets are contraindicated in patients with hypersensitivity to nicorandil or any of the excipients.

Nicorandil must not be used in the case of cardiogenic shock, hypotension or left ventricular failure with low filling pressure.

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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Gastrointestinal ulcerations, skin and mucosal ulceration have been reported with nicorandil (see section 4.8). These are refractory to treatment and most only respond to withdrawal of nicorandil treatment. If ulcerations develop, nicorandil should be discontinued.

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

Nicorandil must be used with caution in patients who may have blood volume depletion or in those who present low systolic blood pressure (e.g. below 100 mm Hg), acute pulmonary oedema or acute myocardial infarction with acute left ventricular failure and low filling pressures.

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

The tablets are sensitive to moisture; hence the patients should be advised to keep the tablets in their blister until intake (see section 6.4).

Paediatric patients

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

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

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.

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy: Although animal studies have not shown any teratogenic effect of nicorandil, the medicinal product has not been studied in human pregnancy; therefore, Nicorandil Tablets must only be used in pregnant women if the anticipated benefit outweighs any potential risks.

Lactation: 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: Nicorandil was not shown to alter fertility in animal studies. There are no human data.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Blood pressure-lowering effects of nicorandil can reduce the ability to drive or to use machines. This effect can be increased in conjunction with alcohol or other products with blood-pressure-lowering effect (e.g. vasodilators, tricyclic antidepressants) (see section 4.5).

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 definitions apply to the frequency terminology used hereafter:

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).

SOC	FREQUENCY	ADR
Nervous system disorders	Very common	Headache, particularly during the first few days of treatment
	Common	Dizziness
Cardiac disorders	Common	Increase in heart rate, following the administration of high doses
Vascular disorders	Common	Cutaneous vasodilation with flushing

	Uncommon	Decrease in blood pressure
Gastrointestinal disorders	Common	Nausea and vomiting
	Rare	Gastrointestinal ulcerations such as stomatitis, mouth ulcers, tongue ulcers, intestinal and anal ulcers. These ulcers, if advanced, may develop into perforation, fistula, or abscess formation (see section 4.4)
Hepato-biliary disorders	Very rare	Liver disorders such as hepatitis, cholestasis, or jaundice
Skin and subcutaneous tissue disorders	Rare	Different types of rash, pruritus
	Very rare	Angio-oedema. Skin and mucosal ulcerations (mainly peri-anal ulcerations, genital ulcerations and parastomal ulcerations) (see section 4.4)
Musculoskeletal & connective tissue disorders	Rare	Myalgia
General disorders and administration site conditions	Common	Feeling of weakness

Additional Information

In addition, the following events have been reported at a different frequency in the IONA (Impact of Nicorandil in Angina) study which was conducted in subjects at high risk of cardiovascular events only.

Skin and subcutaneous tissue disorders

Uncommon – angio-oedema

Gastrointestinal disorders

Common – rectal bleeding

Uncommon – mouth ulcers

Very rare – abdominal pain

Musculoskeletal & connective tissue disorders

Uncommon - myalgia

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 substitution of fluid is recommended. In life-threatening situations, administration of vasopressors must be considered. There is no 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 a 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 \geq 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 2 hours (this differs from the reference product; half-life of the reference product is 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

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

Effects observed in reproductive toxicity studies (increased pre-implantation loss, fetal mortality and peri-natal mortality) and in repeated dose toxicity studies (testicular and skeletal muscle damage in rats and cardiovascular effects in dogs) were seen at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol
Cetyl alcohol
Croscarmellose sodium
Povidone
Sodium stearyl fumarate
Silica colloidal anhydrous

6.2 INCOMPATIBILITIES

Not applicable.

- 6.3 SHELF LIFE**
18 months
- 6.4 SPECIAL PRECAUTIONS FOR STORAGE**
Store below 25°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, 56 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**
- 8 MARKETING AUTHORISATION NUMBER(S)**
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
19/07/2011
- 10 DATE OF REVISION OF THE TEXT**
19/07/2011

1 NAME OF THE MEDICINAL PRODUCT

Nicorandil 20mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Nicorandil 20mg

Each tablet contains 20mg nicorandil.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet, white to off white, round, scored on one side and engraved with "20" on the other side.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS**4.1 THERAPEUTIC INDICATIONS**

Nicorandil 20mg Tablets are indicated for the following:

- The prevention and long term treatment of chronic stable angina pectoris
- A 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 \geq 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

Route of administration: oral.

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 twice daily may be employed if necessary.

Elderly: For elderly patients use of the lowest effective dose is recommended.

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

4.3 CONTRAINDICATIONS

Nicorandil 20mg Tablets are contraindicated in patients with hypersensitivity to nicorandil or any of the excipients.

Nicorandil must not be used in the case of cardiogenic shock, hypotension or left ventricular failure with low filling pressure.

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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Gastrointestinal ulcerations, skin and mucosal ulceration have been reported with nicorandil (see section 4.8). These are refractory to treatment and most only respond to withdrawal of nicorandil treatment. If ulcerations develop, nicorandil should be discontinued.

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

Nicorandil must be used with caution in patients who may have blood volume depletion or in those who present low systolic blood pressure (e.g. below 100 mm Hg), acute pulmonary oedema or acute myocardial infarction with acute left ventricular failure and low filling pressures.

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

The tablets are sensitive to moisture; hence the patients should be advised to keep the tablets in their blister until intake (see section 6.4).

Paediatric patients

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

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

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.

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy: Although animal studies have not shown any teratogenic effect of nicorandil, the medicinal product has not been studied in human pregnancy; therefore, Nicorandil Tablets must only be used in pregnant women if the anticipated benefit outweighs any potential risks.

Lactation: 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: Nicorandil was not shown to alter fertility in animal studies. There are no human data.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Blood pressure-lowering effects of nicorandil can reduce the ability to drive or to use machines. This effect can be increased in conjunction with alcohol or other products with blood-pressure-lowering effect (e.g. vasodilators, tricyclic antidepressants) (see section 4.5).

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 definitions apply to the frequency terminology used hereafter:

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Gastrointestinal disorders	Common	Nausea and vomiting
	Rare	Gastrointestinal ulcerations such as stomatitis, mouth ulcers, tongue ulcers, intestinal and anal ulcers. These ulcers, if advanced,

		may develop into perforation, fistula, or abscess formation (see section 4.4)
Hepato-biliary disorders	Very rare	Liver disorders such as hepatitis, cholestasis, or jaundice
Skin and subcutaneous tissue disorders	Rare	Different types of rash, pruritus
	Very rare	Angio-oedema. Skin and mucosal ulcerations (mainly peri-anal ulcerations, genital ulcerations and parastomal ulcerations) (see section 4.4)
Musculoskeletal & connective tissue disorders	Rare	Myalgia
General disorders and administration site conditions	Common	Feeling of weakness

Additional Information

In addition, the following events have been reported at a different frequency in the IONA (Impact of Nicorandil in Angina) study which was conducted in subjects at high risk of cardiovascular events only.

Skin and subcutaneous tissue disorders

Uncommon – angio-oedema

Gastrointestinal disorders

Common – rectal bleeding

Uncommon – mouth ulcers

Very rare – abdominal pain

Musculoskeletal & connective tissue disorders

Uncommon - myalgia

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 substitution of fluid is recommended. In life-threatening situations, administration of vasopressors must be considered. There is no 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 a 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 \geq 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 2 hours (this differs from the reference product; half-life of the reference product is 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

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

Effects observed in reproductive toxicity studies (increased pre-implantation loss, fetal mortality and peri-natal mortality) and in repeated dose toxicity studies (testicular and skeletal muscle damage in rats and cardiovascular effects in dogs) were seen at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol
Cetyl alcohol
Croscarmellose sodium
Povidone
Sodium stearyl fumarate
Silica colloidal anhydrous

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

18 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

6.5 NATURE AND CONTENTS OF CONTAINER

Nicorandil 20mg Tablets are packed in ALU /ALU blisters with an integrated desiccant layer. The blister strips are packaged in cartons of 10, 28, 56 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

8 MARKETING AUTHORISATION NUMBER(S)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/07/2011

10 DATE OF REVISION OF THE TEXT

19/07/2011

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, please 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 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 Tablets are and what they are used for
2. Before you take Nicorandil Tablets
3. How to take Nicorandil Tablets
4. Possible side effects
5. How to store Nicorandil Tablets
6. Further information

1. WHAT NICORANDIL TABLETS ARE AND WHAT THEY ARE USED FOR

The name of your medicine is Nicorandil 10mg Tablets or Nicorandil 20mg Tablets (referred to as Nicorandil Tablets throughout this leaflet). These tablets contain a medicine called nicorandil. This belongs to a group of medicines called 'potassium-channel activators'.

Nicorandil Tablets work by increasing the blood flow through the blood vessels of the heart.

Nicorandil Tablets are used to prevent and treat long-term chest pain (angina).

2. BEFORE YOU TAKE NICORANDIL TABLETS

Do not take Nicorandil Tablets and tell your doctor if:

- You are allergic (hypersensitive) to nicorandil or any of the other ingredients of Nicorandil Tablets (see section 6 – "Further information").
Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.
- You have low blood pressure (signs include feeling dizzy, light-headed or faint)
- You have a heart problem where the heart is damaged and cannot pump enough blood around the body
- You have heart failure (signs include shortness of breath, swollen ankles and legs, and feeling tired)
- You are taking medicines for erectile dysfunction (impotence) such as sildenafil, tadalafil or vardenafil

Do not take this medicine if any of these apply to you. If you are not sure, talk to your doctor or pharmacist before taking Nicorandil Tablets.

Take special care with Nicorandil Tablets

Check with your doctor or pharmacist before taking this medicine if:

- You have been told by your doctor that you have low blood volume or low systolic blood pressure
- You have recently had a heart attack
- You have a build up of fluid in the lungs (pulmonary oedema)
- You have mouth ulcers

If you are not sure if any of these apply to you, talk to your doctor or pharmacist before taking Nicorandil Tablets.

Taking other medicines

Please tell your doctor or pharmacist if you are taking, or have recently taken, any other medicines. This includes medicines obtained without a prescription, including herbal medicines. This is because Nicorandil Tablets can affect the way some other medicines work. Also some medicines can affect the way Nicorandil Tablets work.

In particular, do not take Nicorandil Tablets, and tell your doctor if you are taking:

- Medicines for erectile dysfunction (impotence) such as sildenafil, tadalafil or vardenafil

Tell your doctor if you are taking any of the following:

- Medicines that widen the blood vessels such as hydralazine, minoxidil or nitroprusside (vasodilators)
- Medicines for high blood pressure
- Medicines for depression
- Medicines for inflammation (corticosteroids such as prednisolone)

Taking Nicorandil Tablets with food and drink

Do not drink alcohol while you are taking Nicorandil Tablets.

Pregnancy and breast-feeding

Talk to your doctor before taking this medicine if you are pregnant, might become pregnant or think you may be pregnant.

You should not breast-feed if you are taking Nicorandil Tablets. This is because small amounts of this medicine may pass into mothers' milk. If you are breast-feeding or planning to breast-feed, talk to your doctor or pharmacist before taking this medicine.

Ask your doctor or pharmacist for advice before taking any medicine if you are pregnant or breast-feeding.

Driving and using machines

You may feel dizzy while taking this medicine. If this happens, do not drive or use any tools or machines.

3. HOW TO TAKE NICORANDIL TABLETS

Always take Nicorandil Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Taking this medicine

- Take this medicine by mouth
- Swallow the tablets whole with a drink of water. Do not crush or chew the tablets
- If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself, but ask your doctor

How much to take

- The usual dose is 10mg or 20mg taken twice a day, once in the morning and once in the evening.
- Your doctor might increase this to 30mg twice a day if necessary.
- If you have tendency to get headaches, your doctor may start you on a lower dose of 5mg (half of a 10mg tablet) twice a day.

Use in children

Nicorandil Tablets are **not** recommended for use in children.

If you take more Nicorandil Tablets than you should

If you take more tablets than you should, tell a doctor or go to a hospital casualty department immediately. Take the medicine pack with you. This is so the doctor knows what you have taken. The following effects may happen: you may feel dizzy or weak or have difficulty in breathing or wheezing.

If you forget to take Nicorandil Tablets

If you forget to take a dose, take it as soon as you remember. However, if it is almost time for you to take your next dose, skip the dose you missed and continue to follow the dosing schedule as usual. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Nicorandil Tablets

Keep taking Nicorandil Tablets until your doctor tells you to stop. Do not stop taking Nicorandil Tablets because you feel better. If you stop, your illness may get worse or come back.

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

4. POSSIBLE SIDE EFFECTS

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

Stop taking Nicorandil Tablets and see a doctor immediately or go to a hospital straight away if you have the following side effects:

Uncommon (affects less than 1 in 100 people)

- Red and lumpy skin rash, swollen eyelids, face, lips, mouth or tongue, itching, difficulty breathing or swallowing. This could be an allergic reaction (angioedema).

Very rare (affects less than 1 in 10,000 people)

- Yellowing of your skin or eyes (which may be signs of liver problems).

Tell your doctor immediately if you have any of the following side effects:

Common (affects less than 1 in 10 people)

- Increased or fast heart-beat

Rare (affects less than 1 in 1000 people)

- Blood in your stools or vomit, due to ulcers in the stomach or gut
- Ulcers of the back passage, bleeding from the back passage

Very rare (affects less than 1 in 10,000 people)

- Ulcers of the genital tract
- Skin ulcers, possibly on the hands, legs, or feet
- Ulcers in the nasal passages
- Ulcers around a stoma (in those with an artificial opening for waste removal such as a colostomy or ileostomy)

Tell your doctor as soon as possible if you have any of the following:

Very common (affects more than 1 in 10 people)

- Headache. These are more common when you first start taking Nicorandil Tablets.

Common (affects less than 1 in 10 people)

- Feeling dizzy or weak
- Feeling sick or being sick
- Flushing of the skin

Uncommon (affects less than 1 in 100 people)

- Feeling lightheaded or fainting (due to low blood pressure)
- Mouth ulcers
- Pain in your muscles

Rare (affects less than 1 in 1000 people)

- Skin rashes

Very rare (affects less than 1 in 10,000 people)

- Stomach pain

Talk to your doctor or pharmacist if any of the side effects gets serious or lasts longer than a few days, or if you notice any side effects not listed in this leaflet.

5. HOW TO STORE NICORANDIL TABLETS

Keep out of the reach and sight of children.

Do not use Nicorandil Tablets after the expiry date which is stated on the blister or carton after EXP. The expiry date refers to the last day of that month.

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

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 Tablets contain

- The active substance is nicorandil. Each 10mg tablet contains 10mg nicorandil. Each 20mg tablet contains 20mg nicorandil.
- The other ingredients are: cetyl alcohol, mannitol, croscarmellose sodium, povidone, silica colloidal anhydrous and sodium stearyl fumarate.

What Nicorandil Tablets look like

The tablets are white to off-white, round, scored on one side and engraved with "10" or "20" on the other side.

The tablets can be divided into equal halves.

Contents of the pack

Nicorandil Tablets are available in packs of 10, 28, 56 and 60 tablets in blister strips. Not all pack sizes may be marketed.

Marketing Authorisation Holder:

Manufacturer: Dexcel[®] - Pharma Ltd., 1 Cottesbrooke Park,
Heartlands Business Park, Daventry, Northamptonshire, NN11 8YL, UK

This leaflet was last approved in July 2011.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**BOX****1. NAME OF THE MEDICINAL PRODUCT**

Nicorandil 10mg / 20mg Tablets

Active Ingredient: Nicorandil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains: 10 mg / 20 mg Nicorandil.

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

10 Tablets

28 Tablets

56 Tablets

60 Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Dosage: for oral use.

Read package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25 °C.

Keep the tablets in the original blister strip in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MARKETING AUTHORISATION HOLDER:

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nicorandil 10mg / 20mg Tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nicorandil 10mg / 20mg Tablets

Nicorandil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER