Public Assessment Report

Decentralised Procedure

Nicorandil 10 mg and 20 mg Tablets

Procedure Nos: UK/H/3857/001-2/DC
                UK/H/4408/001-2/DC

UK Licence Nos: PL 20897/0033-4
                PL 20897/0061-2

Helm AG
LAY SUMMARY

On 04 and 22 August 2011, the MHRA granted Marketing Authorisations to Helm AG for medicines called Nicorandil 10 mg and 20 mg Tablets.

These medicines are available on prescription from your doctor.

Nicorandil may be used to prevent and treat long-term chest pain (angina pectoris). The active ingredient, nicorandil, belongs to a family of medicines called potassium.channel activators. Nicorandil works 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 10 mg and 20 mg Tablets outweigh the risks, and Marketing Authorisations were granted.
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# Module 1

## Information about the initial procedure

| Product Names            | Nicorandil 10 mg Tablets
<table>
<thead>
<tr>
<th></th>
<th>Nicorandil 20 mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Nicorandil</td>
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<tr>
<td><strong>Form</strong></td>
<td>Tablet</td>
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<tr>
<td><strong>Strength</strong></td>
<td>10 mg and 20 mg</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Helm AG</td>
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<td></td>
<td>Nordkanalstr.28</td>
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<tr>
<td></td>
<td>20097 Hamburg</td>
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<tr>
<td></td>
<td>Germany</td>
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<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
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<tr>
<td><strong>Concerned Member States (CMS)</strong></td>
<td>UK/H/3857/001-2/DC: Austria (AT), Germany (DE), Italy (IT) and Portugal (PT)</td>
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<tr>
<td></td>
<td>UK/H/4408/001-2/DC: Bulgaria (BG), the Czech Republic (CZ), Hungary (HU), Lithuania (LT), Latvia (LV), Poland (PL), Romania (RO) and the Slovak Republic (SK)</td>
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<td><strong>Procedure Number</strong></td>
<td>UK/H/3857/001-2/DC</td>
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<td></td>
<td>UK/H/4408/001-2/DC</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 15 June 2011</td>
</tr>
</tbody>
</table>
Module 2
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Nicorandil 10 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Nicorandil 10 mg tablet contains 10 mg nicorandil.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.
White to off-white round, flat tablet with a break line on one side.

Nicorandil 10 mg tablets can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
- The prevention and long term treatment of chronic stable angina pectoris.

4.2 Posology and method of administration
For oral use.

Adults
The recommended starting dose is 10 mg nicorandil twice daily, preferably in the morning and in the evening.

A lower starting dose of 5 mg twice daily may be employed (for a few days) in patients particularly susceptible to headache.

Subsequently the dosage should be titrated upwards depending on the patient’s clinical response and tolerance.

The usual therapeutic dosage is in the range of 10 to 20 mg nicorandil twice daily, although up to 30 mg twice daily may be employed, if necessary.

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

Paediatric Population
Nicorandil 10 mg tablets are not recommended for use in children and adolescents below 18 years due to insufficient data on safety and efficacy.

4.3 Contraindications
Nicorandil 10 mg tablets are contraindicated in patients with hypersensitivity to nicorandil or to 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 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 ulcerations have been reported with nicorandil. These are refractory to treatment and most only respond to withdrawal of nicorandil treatment. If ulcerations develop, it is recommended to discontinue the nicorandil treatment.
Gastrointestinal perforations in 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 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.

**Paediatric patients**

Nicorandil 10 mg is 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

Concurrent use of nicorandil and phosphodiesterase 5 inhibitors, e.g. sildenafil, tadalfil, 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 10 mg 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 10 mg is 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)*
### 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: Angioedema

Gastrointestinal disorders

Common: Rectal bleeding.

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Frequency</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nervous system disorder</strong></td>
<td></td>
<td>Headache, particularly during the first few days of treatment.</td>
<td>Dizziness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
<td>Increase in heart rate, following the administration of high doses.</td>
<td>Tachycardia (at high doses)</td>
<td>Palpitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td>Cutaneous vasodilation with flushing</td>
<td>Decrease in blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td>Nausea, vomiting</td>
<td>Gastrointestinal ulcerations such as aphthosis, mouth ulcers, tongue ulcers, intestinal and anal ulcers. These ulcers, if advanced, may develop into perforation, fistula, or abscess formation. (see section 4.4).</td>
<td></td>
<td></td>
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<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td>Liver disorders such as hepatitis, cholestasis, or jaundice.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td>Different types of rash, pruritis</td>
<td>Angio-oedema, Skin and mucosal ulcerations (mainly peri-anal ulcerations, genital ulcerations and parastomal ulcerations (see section 4.4).</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td>Myalgia</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td>Feeling of weakness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Uncommon: Mouth ulcers
Very Rare: Abdominal pain.

Musculoskeletal and 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 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.

There is no experience of massive overdose in humans. The LD50 of nicorandil in rodents following oral administration is of the order of 1200 mg/kg, and of 62.5-125 mg/kg in dogs.

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 antianginal 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 ≤45%, or an end diastolic dimension of >55 mm, age ≥65 years, 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
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, acute- and 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
Sodium starch glycolate (Type A)
Stearic acid
Mannitol

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
15 months

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
Nicorandil 10 mg tablets are supplied in polyamide /Aluminium/PE/desiccant/PE-Alu/PE blisters of 10 tablets.

Pack size: 20, 30 and 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

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

7 MARKETING AUTHORISATION HOLDER
Helm AG
Nordkanalstr.28
20097 Hamburg
Germany

8 MARKETING AUTHOURISATION NUMBER(S)
PL 20897/0033 and PL 20897/0061

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
04/08/2011 and 22/08/2011

10 DATE OF REVISION OF THE TEXT
04/08/2011 and 22/08/2011
1 NAME OF THE MEDICINAL PRODUCT
Nicorandil 20 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Nicorandil 20 mg tablet contains 20 mg nicorandil.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.
White to off-white round, flat tablet.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
- The prevention and long term treatment of chronic stable angina pectoris.

4.2 Posology and method of administration
For oral use.

Adults
The recommended starting dose is 10 mg nicorandil twice daily, preferably in the morning and in the evening.

A lower starting dose of 5 mg twice daily may be employed (for a few days) in patients particularly susceptible to headache.

Subsequently the dosage should be titrated upwards depending on the patient’s clinical response and tolerance.

The usual therapeutic dosage is in the range of 10 to 20 mg nicorandil twice daily, although up to 30 mg twice daily may be employed, if necessary.

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

Paediatric Population
Nicorandil 20 mg tablets are not recommended for use in children and adolescents below 18 years due to insufficient data on safety and efficacy.

4.3 Contraindications
Nicorandil 20 mg tablets are contraindicated in patients with hypersensitivity to nicorandil or to 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 is contraindicated, since it can lead to a serious drop in blood pressure.

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Paediatric patients
Nicorandil 20 mg is not recommended in paediatric patients since its safety and efficacy have not been established in this patient group.

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

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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 20 mg 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 20 mg is 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).

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**Skin and subcutaneous tissue disorders**

Uncommon: Angioedema
Gastrointestinal disorders
Common: Rectal bleeding.
Uncommon: Mouth ulcers
Very Rare: Abdominal pain.

Musculoskeletal and 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.

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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.

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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**
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, acute- and 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**
Sodium starch glycolate (Type A)
Stearic acid
Mannitol

6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
15 months

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**
Nicorandil 20 mg tablets are supplied in polyamide /Aluminium/PE/desiccant/PE-Alu/PE blisters of 10 tablets.

Pack size: 20, 30 and 60 tablets.

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements.

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

7 **MARKETING AUTHORISATION HOLDER**
Helm AG
Nordkanalstr.28
20097 Hamburg
Germany

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9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
04/08/2011 and 22/08/2011

10 **DATE OF REVISION OF THE TEXT**
04/08/2011 and 22/08/2011
Module 3
Patient Information Leaflet
The Patient Information Leaflets (PILs) below are the leaflets for PL 20897/0033-4 only. Please note that there are no mock-ups available for PL 20897/0061-2. The marketing authorisation holder has stated that it is not intending to market the products and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK PILs for review to the regulatory authority before marketing the products.

PACKAGE LEAFLET: INFORMATION FOR THE USER
Noricandil 10 mg tablets

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 gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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

1. WHAT NORICANDIL IS AND WHAT IT IS USED FOR
Noricandil contains a substance called nicorandil. This substance belongs to a group of medicines called “potassium channel activators”. It works by relaxing blood vessels and increasing the blood flow and oxygen supply to the heart.

Noricandil is used
- to prevent chest pain (angina pectoris)
- for long-term treatment of chest pain (stable angina pectoris)

2. BEFORE YOU TAKE NORICANDIL
Do not take Noricandil
- If you are allergic (hypersensitive) to nicorandil or any of the other ingredients of Noricandil
- If you have a condition called “cardiogenic shock”. This is a severe drop in blood pressure, caused by the fact that the heart cannot pump enough blood around the body.

These medicines are also used for a rare progressive disease of the blood vessels in the lung (pulmonary arterial hypertension). The simultaneous use of these medicines and Noricandil can lead to a serious drop in blood pressure.

Tell your doctor if you are taking any of the following:
- medicines that widen the blood vessels (vasodilators)
- medicines used to treat high blood pressure
- medicines used to treat depression (tricyclic antidepressants)

If you take one of these medicines together with Noricandil your blood pressure could get too low.

If you take Noricandil together with corticosteroids (medicines used to treat inflammation), perforations in the stomach or gut can occur.

Taking Noricandil with food and drink
Do not drink alcohol while you are taking Noricandil. This is because Noricandil may increase the effect of alcohol.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

Noricandil should not be used during pregnancy unless your doctor considers that it is clearly necessary.

You should not use nicorandil if you are breast-feeding because it is not known whether nicorandil is excreted into human breast milk.

Driving and using machines
Since Noricandil lowers your blood pressure, you may feel dizzy or light-headed while taking this medicine. If this happens, do not drive or use any tools or machines.

3. HOW TO TAKE NORICANDIL

15
- if you have a heart failure and your left side of the heart fails to pump blood effectively (left ventricular failure with low filling pressures)
- if you have low blood pressure
- together with medicines for impotence (see also "Taking other medicines")

Take special care with Nicorandil
- if you have ulcers in the stomach or gut
- if you have skin ulcers
- if you have mouth ulcers
- if you have been told by your doctor that you have a low blood volume or low systolic blood pressure
- if you have an acute build up of fluid in the lungs (acute pulmonary oedema)
- if you have recently had a heart attack (acute myocardial infarction)

Inform your doctor before treatment if any of the above mentioned conditions apply to you.

Taking 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.

You must not take Nicorandil, and tell your doctor, if you are taking medicines for impotence such as sildenafil, tadalafil or vardenafil (phosphodiesterase 5 inhibitors).

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

Method of administration
Take this medicine by mouth. Swallow the tablets whole with a sufficient amount of water (e.g. one glass of water). You can take the tablets with or without food. Do not crush or chew the tablets.

Dosage
Take 1 to 2 tablets in the morning and in the evening (equivalent to a daily dose of 20 to 40 mg of Nicorandil). Your doctor might increase this to 3 tablets twice a day, if necessary (equivalent to a daily dose of 60 mg of nicorandil).

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

Use in children
Nicorandil is not recommended for use in children and adolescents below 18 years due to insufficient data on safety and efficacy.

Elderly patients
Elderly patients should take the lowest possible dose that relieves the complaints.
Your doctor will decide how many tablets of Nicorandil you will have to take per day.

If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself, but talk to your doctor.

**If you take more Nicorandil than you should**
If you take more tablets than you should, or if a child has swallowed any of your tablets, tell a doctor or go to a hospital casualty department straight away. Take the medicine pack with you. This is so the doctor knows what you have or the child has taken. The following effects may happen: your blood pressure drops off and you may feel dizzy or weak, your heart may beat faster than normal or you have difficulty in breathing or wheezing.

**If you forget to take Nicorandil**
If you forget a dose, take it as soon as you remember it. However, if it is nearly time for the next dose, skip the missed dose. Do not take a double dose to make up for a forgotten tablet.

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

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

d) Tell your doctor as soon as possible if you have any of the following side effects:

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

**Common**
- Dizziness
- Increased heartbeat
- Flushing of the skin
- Feeling sick or being sick
- Feeling weak

**Uncommon**
- Decrease in blood pressure (feeling dizzy, lightheaded or fainting)

**Rare**
- Skin rashes
- Itching
- Pain in your muscles

e) Other side effects

Very rare
- Belly ache

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

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 label carton and blister after EXP.
4. POSSIBLE SIDE EFFECTS

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

Assessment of side effects is based on the following frequency rates:

very common: affects more than 1 user in 10
common: affects 1 to 10 users in 100
uncommon: affects 1 to 10 users in 1,000
rare: affects 1 to 10 users in 10,000
very rare: affects less than 1 user in 10,000

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

Very rare
- Yellowing of your skin or eyes (which may be signs of liver problems)
- Red and lumpy skin rash, swollen eyelids, face, lips, mouth or tongue, itching, difficulty breathing or swallowing. This could be an allergic reaction (angioedema)

b) Stop taking Nicorandil and see your doctor if you develop ulcerations. These ulcerations cannot medicinally be treated and they only respond if you discontinue the treatment with Nicorandil:

Rare
- Blood in your stools or vomit (due to ulcers in the stomach or gut), mouth ulcers, tongue ulcers, ulcers of the anus, or bleeding from the anus

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

c) Tell a doctor straight away if you have any of the following side effects

Common
- Increased or fast heart-beat (Palpitation)

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.

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. Each tablet contains 10 mg nicorandil.
- The other ingredients are sodium starch glycolate (type A), stearic acid, mannitol.

What Nicorandil looks like and contents of the pack
Nicorandil tablets are white to off-white round, flat tablets with a break line on one side.

The tablets can be divided into equal halves.

They are supplied in blisters of 20, 30 or 60 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Helm AG, Nordkanaalstrasse 28, 20097 Hamburg, Germany

Manufacturer
Bluepharma Indústria Farmacêutica, S.A
Cimo de Fala – S. Martinho do Bispo, 3045-016 Coimbra Portugal

This medicinal product is authorised in the Member States of the EEA under the following names

United Kingdom: Nicorandil 10 mg tablets
Spain: Nicorandil Petazone 10 mg comprimidos
Germany, Netherlands: Doranic 10 mg Tabletten
Italy: Doranic 10 mg compresse
Portugal: Doranic 10 mg comprimidos
Denmark: Nicozone 10 mg tabletter
Ireland: Nicozone 10 mg tablets

This leaflet was last approved in 06/2011.
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 gets 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 contains a substance called nicorandil. This substance belongs to a group of medicines called “potassium channel activators”. It works by relaxing blood vessels and increasing the blood flow and oxygen supply to the heart.

Nicorandil is used
- to prevent chest pain (angina pectoris)
- for long-term treatment of chest pain (stable angina pectoris)

These medicines are also used for a rare progressive disease of the blood vessels in the lung (pulmonary arterial hypertension). The simultaneous use of these medicines and Nicorandil can lead to a serious drop in blood pressure.

Tell your doctor if you are taking any of the following:
- medicines that widen the blood vessels (vasodilators)
- medicines used to treat high blood pressure
- medicines used to treat depression (tricyclic antidepressants)

If you take one of these medicines together with Nicorandil your blood pressure could get too low.

If you take Nicorandil together with corticosteroids (medicines used to treat inflammation), perforations in the stomach or gut can occur.

Taking Nicorandil with food and drink
Do not drink alcohol while you are taking Nicorandil. This is because Nicorandil may increase the effect of alcohol.

Pregnancy and breast-feeding

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

Nicorandil should not be used during pregnancy unless your doctor considers that it is clearly necessary.
2. BEFORE YOU TAKE NICORANDIL

Do not take Nicorandil
- If you are allergic (hypersensitive) to nicorandil or any of the other ingredients of Nicorandil
- If you have a condition called “cardio-genic shock”. This is a severe drop in blood pressure, caused by the fact that the heart cannot pump enough blood around the body
- If you have a heart failure and your left side of the heart fails to pump blood effectively (left ventricular failure with low filling pressures)
- If you have low blood pressure
- Together with medicines for impotence (see also “Taking other medicines”)

Take special care with Nicorandil
- If you have ulcers in the stomach or gut
- If you have skin ulcers
- If you have mouth ulcers
- If you have been told by your doctor that you have a low blood volume or low systolic blood pressure
- If you have an acute build up of fluid in the lungs (acute pulmonary oedema)
- If you have recently had a heart attack (acute myocardial infarction)
Inform your doctor before treatment if any of the above mentioned conditions apply to you.

Taking 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.

You must not take Nicorandil, and tell your doctor, if you are taking medicines for impotence such as sildenafil, tadalafil or vardenafil (phosphodiesterase 5 inhibitors).

You should not use nicorandil if you are breast-feeding because it is not known whether nicorandil is excreted into human breast milk.

Driving and using machines
Since Nicorandil lowers your blood pressure, you may feel dizzy or light-headed while taking this medicine. If this happens, do not drive or use any tools or machines.

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.

Method of administration
Take this medicine by mouth. Swallow the tablets whole with a sufficient amount of water (e.g. one glass of water). You can take the tablets with or without food. Do not crush or chew the tablets.

Dosage
The usual dose is 10mg or 20mg taken in the morning and in the evening (equivalent to a daily dose of 20 to 40 mg of nicorandil). Your doctor might increase this to 30 mg twice a day, if necessary (equivalent to a daily dose of 60 mg of nicorandil).

If you have a tendency to get headaches, your doctor may start you on a lower dose of 5 mg nicorandil twice a day (equivalent to 10 mg of nicorandil). Therefore you can get Nicorandil 10 mg tablets, that can be divided into equal halves with 5 mg nicorandil each.

Use in children
Nicorandil is not recommended for use in children and adolescents below 18 years due to insufficient data on safety and efficacy.

continued overleaf
Elderly patients
Elderly patients should take the lowest possible dose that relieves the complaints. Your doctor will decide how many tablets of Nicorandil you will have to take per day.

If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself, but talk to your doctor.

If you take more Nicorandil than you should
If you take more tablets than you should, or if a child has swallowed any of your tablets, tell a doctor or go to a hospital casualty department straight away. Take the medicine pack with you. This is so the doctor knows what you have or the child has taken. The following effects may happen: your blood pressure drops off and you may feel dizzy or weak, your heart may beat faster than normal or you have difficulty in breathing or wheezing.

If you forget to take Nicorandil
If you forget a dose, take it as soon as you remember it. However, if it is nearly time for the next dose, skip the missed dose. Do not take a double dose to make up for a forgotten tablet.

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

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

d) Tell your doctor as soon as possible if you have any of the following side effects:

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

Common
- Dizziness
- Increased heartbeat
- Flushing of the skin
- Feeling sick or being sick
- Feeling weak

Uncommon
- Decrease in blood pressure (feeling dizzy, lightheaded or fainting)

Rare
- Skin rashes
- Itching
- Pain in your muscles

e) Other side effects

Very rare
- Belly ache

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

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 label carton and blister after EXP.
4. POSSIBLE SIDE EFFECTS

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

Assessment of side effects is based on the following frequency rates:

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

Very rare
- Yellowing of your skin or eyes (which may be signs of liver problems)
- Red and lumpy skin rash, swollen eyelids, face, lips, mouth or tongue, itching, difficulty breathing or swallowing. This could be an allergic reaction (angioedema).

b) Stop taking Nicorandil and see your doctor if you develop ulcerations. These ulcers cannot medicinally be treated and they only respond if you discontinue the treatment with Nicorandil:

Rare
- Blood in your stools or vomit (due to ulcers in the stomach or gut), mouth ulcers, tongue ulcers, ulcers of the anus, or bleeding from the anus

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

c) Tell a doctor straight away if you have any of the following side effects

Common
- Increased or fast heart-beat (Palpitation)

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.

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. Each tablet contains 20 mg nicorandil.
- The other ingredients are sodium starch glycolate (type A), stearic acid, mannitol.

What Nicorandil looks like and contents of the pack
Nicorandil tablets are white to off-white round and flat
They are supplied in blisters of 20, 30 or 60 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
Helm AG, Nordkanalstrasse 28, 20097 Hamburg, Germany

Manufacturer
Bluepharma Indústria Farmacêutica, S.A
Cimo de Fala – S. Martinho do Bispo, 3045-016 Coimbra Portugal

This medicinal product is authorised in the Member States of the EEA under the following names

United Kingdom: Nicorandil 20 mg tablets
Spain: Nicorandil Petazone 20 mg comprimidos
Germany, Netherlands: Doranic 20 mg Tabletten
Italy: Doranic 20 mg compresse
Portugal: Doranic 20 mg comprimidos
Denmark: Nicozone 20 mg tabletter
Ireland: Nicozone 20 mg tablets

This leaflet was last approved in 06/2011.
Module 4
Labelling

An example of the labelling text for PL 20897/0033-4 is below. Please note that there are no labelling mock-ups available. The marketing authorisation holder has stated that it is not intending to market the products and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK labelling for review to the regulatory authority before marketing the products.

Cartons:

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. NAME OF THE MEDICINAL PRODUCT</td>
</tr>
<tr>
<td>Nicorandil 10 mg tablets</td>
</tr>
<tr>
<td>Nicorandil 20 mg tablets</td>
</tr>
<tr>
<td>Nicorandil</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each tablet contains 10 mg nicorandil.</td>
</tr>
<tr>
<td>Each tablet contains 20 mg nicorandil.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
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<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
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</thead>
<tbody>
<tr>
<td>20 tablets</td>
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<tr>
<td>30 tablets</td>
</tr>
<tr>
<td>60 tablets</td>
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</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
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<tbody>
<tr>
<td>Oral use.</td>
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<tr>
<td>Read the package leaflet before use.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the reach and sight of children.</td>
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<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
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<th>8. EXPIRY DATE</th>
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<tr>
<td>Exp</td>
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</table>

<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
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<tbody>
<tr>
<td>Do not store above 25°C. Store in the original package in order to protect from moisture.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</th>
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</table>

<table>
<thead>
<tr>
<th>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
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Nicorandil 10 mg and 20 mg tablets

Helm AG
Nordkanalstr. 28
20097 Hamburg
Germany

<table>
<thead>
<tr>
<th>12. MARKETING AUTHORISATION NUMBER(S)</th>
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<tr>
<td>PL 20897/0033</td>
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<tr>
<td>PL 20897/0034</td>
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<table>
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<tr>
<th>13. BATCH NUMBER</th>
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<tbody>
<tr>
<td>Lot.</td>
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<table>
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<tr>
<th>14. GENERAL CLASSIFICATION FOR SUPPLY</th>
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<tbody>
<tr>
<td>POM</td>
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<tr>
<th>15. INSTRUCTIONS ON USE</th>
</tr>
</thead>
</table>

<table>
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<tr>
<th>16. INFORMATION IN BRAILLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicorandil 10 mg tablets</td>
</tr>
<tr>
<td>Nicorandil 20 mg tablets</td>
</tr>
</tbody>
</table>
Blister:

<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

   Nicorandil 10 mg tablets  
   Nicorandil 20 mg tablets  
   Nicorandil

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

   Helm AG

3. **EXPIRY DATE**

   Exp.

4. **BATCH NUMBER**

   Lot.

5. **OTHER**
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Nicorandil 10 mg and 20 mg tablets (PL 20897/0033-4 and 0061-2; UK/H/3857 and 4408/001-2/DC) could be approved. The products are prescription-only medicines (POM) indicated for the prevention and long term treatment of chronic stable angina pectoris.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Austria, Bulgaria, the Czech Republic, Germany, Hungary, Italy, Lithuania, Latvia, Poland, Portugal, Romania and the Slovak Republic as Concerned Member States (CMS). The applications were submitted under Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Ikorel 10 mg Tablets and 20 mg Tablets (Sanofi-Aventis, France), which were first authorised in France on 12 August 1992.

The corresponding reference products in the UK are also Ikorel 10mg and 20mg Tablets first authorised in the UK to May and Baker Limited on 6 June 1994 (PL 00012/0229-30). These licences then underwent a change of ownership to Aventis Pharma Limited on 24 February 2009 (PL 04425/0327-8).

The active ingredient, nicorandil is a nitrate ester with potassium channel activating nicotinamide moiety. It is an anti-anginal medication which has a dual mechanism of action: The nicotinamide moiety acts as an opener of ATP-sensitive potassium channels, the NO2 group explains its nitrate-like properties. The nitric oxide-like action leads to a dilatation of the large coronary arteries, whereas its potassium channel opening action is responsible for the dilatation of coronary resistance vessels. Nicorandil has a direct effect on coronary arteries without leading to a steal phenomenon.

Nicorandil has also been found to dilate veins, enabling it to decrease both preload and afterload and to increase coronary blood flow. The overall action improves blood flow to post-stenotic regions and the oxygen balance in the myocardium. The ATP-sensitive potassium channel opening mimics preconditioning in the absence of ischemia and may therefore exert cytoprotective effects. These have been thought to be the reason for a reduction in major coronary events and all cardiovascular events of nicorandil in addition to a specific anti-anginal medication in the Impact of Nicorandil in Angina study (the IONA study). The IONA study reported a reduction of coronary heart disease complications in patients suffering from angina pectoris who were treated with nicorandil.

No new non-clinical data have been submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

A bioequivalence study was submitted to support these applications, comparing the test product Nicorandil 20 mg Tablets (Helm AG) and the reference product Ikorel 20 mg tablets (Sanofi-Aventis, France). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).
With the exception of the bioequivalence study, no new clinical studies were performed, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th><strong>Name of the product in the Reference Member State</strong></th>
<th>Nicorandil 10 mg tablets Nicorandil 20 mg tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name(s) of the active substance(s) (INN)</strong></td>
<td>Nicorandil</td>
</tr>
<tr>
<td><strong>Pharmacotherapeutic classification (ATC code)</strong></td>
<td>Other vasodilators used in cardiac disease (C01DX16)</td>
</tr>
<tr>
<td><strong>Pharmaceutical form and strength(s)</strong></td>
<td>Tablets 10 mg and 20 mg</td>
</tr>
<tr>
<td><strong>Reference numbers for the Decentralised Procedure</strong></td>
<td>UK/H/3857/001-2/DC UK/H/4408/001-2/DC</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>United Kingdom</td>
</tr>
<tr>
<td><strong>Concerned Member States (CMS)</strong></td>
<td>UK/H/3857/001-2/DC: Austria (AT), Germany (DE), Italy (IT) and Portugal (PT)</td>
</tr>
<tr>
<td></td>
<td>UK/H/4408/001-2/DC: Bulgaria (BG), the Czech Republic (CZ), Hungary (HU), Lithuania (LT), Latvia (LV), Poland (PL), Romania (RO) and the Slovak Republic (SK)</td>
</tr>
<tr>
<td><strong>Marketing Authorisation Number(s)</strong></td>
<td>PL 20897/0033 PL 20897/0034</td>
</tr>
<tr>
<td></td>
<td>PL 20897/0061 PL 20897/0062</td>
</tr>
<tr>
<td><strong>Name and address of the Authorisation Holder</strong></td>
<td>Helm AG Nordkanalstr.28 20097 Hamburg Germany</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE
INN: Nicorandil
Chemical names: \( N\)-\[2-(Nitro-oxy)ethyl\]-3-pyridine carboxamide

Structure:

\[
\text{Structure:}
\]

Molecular formula: \( C_8H_9N_3O_4 \)
Molecular Mass: 211.18 g/mol
Appearance: A white off-white crystalline powder. It is freely soluble in acetone, methanol, ethanol and ACN; soluble in ethyl acetate and chloroform; sparingly soluble in water; and slightly soluble in ether.

Nicorandil complies with the European Pharmacopoeia monograph.

Synthesis of the active 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.

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 substance. 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.

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

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

MEDICINAL PRODUCT
Other Ingredients
Other ingredients consist of the pharmaceutical excipients, namely sodium starch glycolate (Type A), stearic acid and mannitol.

All excipients comply with their respective European Pharmacopoeia monographs. All of the excipients used in the production of the Nicorandil 10 mg and 20 mg Tablets are common excipients used in the pharmaceutical manufacture. Therefore, specifications and Certificates of Analysis are not provided.
None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical Development**
The objective of the development programme was to produce safe, efficacious, nicorandil containing products that could be considered generic medicinal products of Ikorel 10 mg Tablets and 20 mg (Sanofi-Aventis, France).
Suitable pharmaceutical development data have been provided for these applications.

Comparative *in-vitro* dissolution and impurity profiles have been provided for these products and their respective reference products.

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of all strengths of the product, along with an appropriate account of the manufacturing process. Based on production-scale batches, the manufacturing process has been validated and has shown satisfactory results.

**Finished Product Specification**
The finished product specifications proposed for all strengths are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

**Container-Closure System**
The products are packaged in blisters composed of polyamide, aluminium and polyethylene (PE) with desiccant.
Pack sizes are 20, 30 and 60 tablets.
Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations.

**Stability of the Product**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 15 months, with the storage conditions “Do not store above 25°C. Store in the original package to protect from moisture.”

**Bioequivalence/Bioavailability**
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

**Summaries of Product Characteristics (SmPCs), Patient Information Leaflets (PILs), Labels**
The SmPCs, PILs and labels are pharmaceutically acceptable.

A package leaflets have 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, as amended. The results indicate that the package leaflets are 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 they contains.

**MAA Forms**
The MAA forms are pharmaceutically satisfactory.

**Expert Report**
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
The grant of these Marketing Authorisations is recommended from a quality point of view.
III.2 NON-CLINICAL ASPECTS

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

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ non-clinical pharmacology, pharmacokinetics and toxicology.

A satisfactory environmental risk assessment was submitted which concluded that no special precautionary and safety measures need to be considered regarding the environmental release from use in patients. Disposal of unused or waste materials derived from nicorandil should be handled according to local disposal protocols.

There are no objections to the approval of these products from a non-clinical point of view.
III.3 CLINICAL ASPECTS
CLINICAL PHARMACOLOGY

The clinical pharmacology of nicorandil is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

Pharmacokinetics
In support of the applications, the Marketing Authorisation Holder submitted the following bioequivalence study:

A randomized, open-label, two-way, crossover study comparing the pharmacokinetics of the test product Nicorandil 20 mg Tablets (Helm AG) and the reference product Ikorel 20 mg tablets (Sanofi-Aventis, France) in healthy subjects, under fasting conditions.

The subjects were given a single 20 mg dose of either treatment after a period of fast. Blood samples were collected before and up to 8 hours after each administration. The washout period between the two treatment arms was 7 days. The pharmacokinetic results are presented below:

The pharmacokinetic parameters (geometric mean ± SD, ratio and confidence intervals [CI]) of nicorandil:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nicorandil 20 mg Tablets (Test)</th>
<th>Ikorel 20 mg Tablets (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>440.99 ± 196.13</td>
<td>411.87 ± 161.35</td>
<td>105.90</td>
<td>93.93-119.39%</td>
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<tr>
<td>$AUC_{0-t}$ (hr.ng/mL)</td>
<td>727.11 ± 156.76</td>
<td>687.54 ± 142.17</td>
<td>105.89</td>
<td>102.65-109.23%</td>
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<tr>
<td>$AUC_{0-\infty}$ (hr.ng/mL)</td>
<td>734.24 ± 157.56</td>
<td>690.06 ± 143.18</td>
<td>106.49</td>
<td>103.15-109.93%</td>
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The Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) defines the confidence limits as 80% to 125% for $C_{\text{max}}$ and $AUC$ values. The 90% confidence intervals of the test/reference ratio of geometric means for $AUC_{0-t}, AUC_{0-\infty}$ and $C_{\text{max}}$ lie within the acceptable limits. Thus, the data support the claim that the test product Nicorandil 20 mg Tablets (Helm AG) is bioequivalent to the reference product Ikorel 20 mg Tablets (Sanofi-Aventis, France)

As the 10 mg and 20 mg strength products meet all the criteria specified in the Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), the results and conclusions from the bioequivalence study with the 20 mg tablet strengths can be extrapolated to the 10 mg tablet strength.

Efficacy
The efficacy of nicorandil is well-known. No new efficacy data have been submitted and none are required for applications of this type.
SAFETY
With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues were raised by the bioequivalence data.

Summary of Product Characteristics (SmPCs), Patient Information Leaflets (PILs), Labels
The SmPCs, PILs and labels are clinically acceptable. The SmPCs are consistent with those for the originator products. The PILs are consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

Clinical Expert Report
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
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.

Suitable justification has been provided for the absence of a risk management plan for these products.

Conclusion
The grant of these Marketing Authorisations is recommended from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Nicorandil 10 mg and 20 mg 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. As the pharmacokinetics, pharmacodynamics and toxicology of nicorandil are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s 20 mg strength tablets and the reference product. As the 10 mg and 20 mg strengths of the product meet all the criteria specified in the Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), the results and conclusions from the bioequivalence study with the 20 mg tablet strength can be extrapolated to the 10 mg tablet strength.

SAFETY
With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for applications of this type. No new or unexpected safety concerns arose from the bioequivalence study.

PRODUCT LITERATURE
The SmPCs, PILs and labelling are acceptable. The SmPCs are consistent with those for the reference products. The PILs are consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data provided support the claim that these products are generic medicinal products of the reference products, Ikorel 10 mg and 20 mg Tablets (Sanofi-Aventis, France). Extensive clinical experience with nicorandil is considered to have demonstrated the therapeutic value of the products. The benefit/risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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