Public Assessment Report

Decentralised Procedure

Nicorandil 10 mg and 20 mg Tablets

Procedure Nos: UK/H/3431/001-2/DC

UK Licence Nos: PL 31623/0059-60

Dexcel Pharma Laboratories Limited
Lay Summary

On 28 June 2011, the MHRA granted Marketing Authorisations to Dexcel Pharma Laboratoires Limited 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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   4 Clinical aspects
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Module 6  Steps taken after initial procedure
## Module 1

### Information about the initial procedure

| **Product Names** | Nicorandil 10 mg Tablets  
Nicorandil 20 mg Tablets |
<table>
<thead>
<tr>
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<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>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Tablet</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>10 mg and 20 mg</td>
</tr>
</tbody>
</table>
| **MA Holder** | Dexcel Pharma Laboratories Limited  
Ashacres House, Ashacres Industrial Park, Draycott in the Clay, Ashbourne, Derbyshire DE6 5GX  
United Kingdom |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | Austria, Czech Republic, France, Hungary, Ireland, Poland, Portugal, Romania and Slovakia |
| **Procedure Number** | UK/H/3431/001-2/DC |
| **Timetable** | Day 210 – 08 June 2011 |
Module 2
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 prevention and long term treatment of chronic stable angina pectoris

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).

<table>
<thead>
<tr>
<th>SOC</th>
<th>FREQUENCY</th>
<th>ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Very common</td>
<td>Headache, particularly during the first few days of treatment</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Dizziness</td>
</tr>
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<td>Common</td>
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<tr>
<td>Uncommon</td>
<td></td>
<td>Decrease in blood pressure</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Rare</td>
<td></td>
<td>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)</td>
</tr>
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<td>SOC</td>
<td>FREQUENCY</td>
<td>ADR</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>-----------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td>Very rare</td>
<td>Liver disorders such as hepatitis, cholestatic, or jaundice</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rare</td>
<td>Different types of rash, pruritus</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Angio-oedema. Skin and mucosal ulcerations (mainly peri-anal ulcerations, genital ulcerations and parastomal ulcerations) (see section 4.4)</td>
</tr>
<tr>
<td>Musculoskeletal &amp; connective tissue disorders</td>
<td>Rare</td>
<td>Myalgia</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common</td>
<td>Feeling of weakness</td>
</tr>
</tbody>
</table>

**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 LD$_{50}$ 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 ≤ 45%, or an end diastolic dimension of ≥ 55 mm, age ≥ 65, diabetes (either type 1 or type 2), hypertension, peripheral vascular disease, or cerebrovascular disease. Patients were excluded from the study if they were receiving a sulphonylurea as it was felt these patients may not benefit; (sulphonylurea agents have the potential to close potassium channels and may thus antagonise some of the effects of nicorandil). Study follow up for endpoint analysis was between 12 and 36 months with a mean of 1.6 years.

The primary endpoint of coronary heart disease (CHD) death, non-fatal myocardial infarction, or unplanned hospital admission for cardiac chest pain, occurred in 13.1% of patients treated with nicorandil compared with 15.5% of patients receiving placebo (hazard ratio 0.83, p=0.014). The rate of acute coronary syndrome (CHD death, non fatal MI or unstable angina), which was a post hoc endpoint, 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). There was no significant reduction in CHD death or in non-fatal myocardial infarction alone. 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. 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 perinatal 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.

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For a full list of excipients, see section 6.1.

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be employed in patients particularly susceptible to headache. Subsequently the dosage should be
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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.

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Noricandil 10mg Tablets are contraindicated in patients with hypersensitivity to nicorandil or any of
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Concurrent use of nicorandil and phosphodiesterase 5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) is
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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.

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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).

Liver disorders such as hepatitis, cholestasis, or jaundice.

Different types of rash, pruritus.

Angio-oedema. Skin and mucosal ulcerations (mainly peri-anal ulcerations, genital ulcerations and parastomal ulcerations) (see section 4.4).

Myalgia.

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
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5.3 Preclinical safety data
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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.
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6.1 List of excipients
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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.

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28/06/2011

10 DATE OF REVISION OF THE TEXT
28/06/2011
Module 3

The Marketing Authorisation Holder has committed to submitting a Change of Ownership to Dexcel Pharma Limited at the earliest opportunity. Hence, there are no UK Specific 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.

Patient Information Leaflet

Noricandil

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:**

**Very rare** (affects less than 1 in 10,000 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).
- 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 June 2011.
Module 4

The Marketing Authorisation Holder has committed to submitting a Change of Ownership to Dexcel Pharma Limited at the earliest opportunity. Hence, there are no UK Specific 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.

Labelling

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 AUTHORITY: 

12. MARKETING AUTHORITY NUMBER(S)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nicorandil 10mg / 20mg Tablets
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<th>Nicorandil 10mg / 20mg Tablets</th>
<th>Nicorandil</th>
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<td><strong>2. NAME OF THE MARKETING AUTHORITY</strong></td>
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<tr>
<td><strong>3. EXPIRY DATE</strong></td>
<td>EXP</td>
<td></td>
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<td><strong>4. BATCH NUMBER</strong></td>
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<td><strong>5. OTHER</strong></td>
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</table>

*Please note that there are no product licence numbers or Marketing Authorisation Holder details on the 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.*
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 31623/0059-60; UK/H/3431/001-2/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, Czech Republic, France, Hungary, Ireland, Poland, Portugal, Romania and Slovakia 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 10 mg Tablets and Ikorel 20 mg Tablets, which were first authorized to Sanofi-Aventis in the UK on 06 June 1994.

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 NO$_2$ 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 single-dose, bioequivalence study was submitted to support these applications, comparing the test product Nicorandil 20 mg Tablets (Dexcel Pharma Laboratories Limited) and the reference product Ikorel 20 mg tablets (Sanofi-Aventis, UK). 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.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates, satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites. The RMS and CMS considered that the applications could be approved at the end of procedure (Day 210) on 08 June 2011. After a subsequent national phase, licences were granted in the UK on 28 June 2011.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Nicorandil 10 mg tablets  
Nicorandil 20 mg tablets |
| Name(s) of the active substance(s) (INN) | Nicorandil |
| Pharmacotherapeutic classification (ATC code) | Other vasodilators used in cardiac disease (C01DX16) |
| Pharmaceutical form and strength(s) | Tablets  
10 mg and 20 mg |
| Reference numbers for the Decentralised Procedure | UK/H/3431/001-2/DC |
| Reference Member State (RMS) | United Kingdom |
| Concerned Member States (CMS) | Austria, Czech Republic, France, Hungary, Ireland, Poland, Portugal, Romania and Slovakia |
| Marketing Authorisation Number(s) | PL 31623/0059-60 |
| Name and address of the Authorisation Holder | Dexcel Pharma Laboratories Limited  
Ashacres House, Ashacres Industrial Park, Draycott in the Clay, Ashbourne, Derbyshire DE6 5GX, United Kingdom |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

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

Structure:

\[
\begin{aligned}
&\text{Structure Image}
\end{aligned}
\]

Molecular formula: \( \text{C}_{3}\text{H}_{9}\text{N}_{3}\text{O}_{4} \)
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 was not the subject of a European Pharmacopoeia monograph at the time of assessment.

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 stearyl fumarate, Cetyl alcohol, Povidone K30 Croscarmellose sodium, Silica colloidal anhydrous 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. The Certificates of Analysis are 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 products that could be considered generic medicinal products of Ikorel 10 mg Tablets and 20 mg (Sanofi-Aventis, UK).

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 two full-scale blend batches and a pilot-scale batch, 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 tablets are packaged in aluminium/aluminium blister strips with an integrated desiccant layer in pack sizes of 10, 28, 56, and 60 tablets.

Not all pack sizes may be marketed. However, the Marketing Authorisation holder has committed to submitting mock-ups to the relevant regulatory authorities for approval before marketing any pack size.

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

**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 18 months, with the storage conditions “Store below 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 Leaflet (PIL), Labels**

The SmPCs, PIL and labels are pharmaceutically acceptable.

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

The Marketing Authorisation Holder has committed to submitting a Change of Ownership to Dexcel Pharma Limited at the earliest opportunity. Hence, there are no UK Specific 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.

**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 Marketing Authorisations is recommended.
III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of nicorandil well-known, no further non-clinical studies are required and none have been provided.

The 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.

As these products are intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated and no suitable justification has been provided for non-submission of an environmental risk assessment.

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

CLINICAL PHARMACOLOGY

The clinical pharmacology of nicorandil is well-known. With the exception of data from the bioequivalence study 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, single-dose, open-label, two-way, crossover study comparing the pharmacokinetics of the test product Nicorandil 20 mg Tablets (Dexcel Pharma Laboratoires Limited) and the reference product Ikorel 20 mg tablets (Sanofi-Aventis, UK) in healthy subjects, under fasting conditions.

The subjects were given a single 20 mg dose of either treatment after at least a 10-hour fast. Blood samples were collected before and up to 12 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&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>484.71 ± 172.18</td>
<td>482.35 ± 208.86</td>
<td>1.04</td>
<td>0.89-1.23%</td>
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<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (hr-ng/mL)</td>
<td>500.87 ± 110.69</td>
<td>518.26 ± 108.61</td>
<td>0.97</td>
<td>0.92-1.01%</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (hr-ng/mL)</td>
<td>511.44 ± 110.46</td>
<td>526.75 ± 109.68</td>
<td>0.97</td>
<td>0.93-1.02%</td>
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</table>

The Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) defines the confidence limits as 80% to 125% for C<sub>max</sub> and AUC values as proof of bioequivalence. The 90% confidence intervals of the test/reference ratio of geometric means for AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub> lie within the acceptable limits. Thus, the data support the claim that the test product Nicorandil 20 mg Tablets (Dexcel Pharma Laboratories Limited) is bioequivalent to the reference product Ikorel 20 mg Tablets (Sanofi-Aventis, UK).

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 (SmPC), Patient Information Leaflet (PIL), Labels
The SmPCs, PIL and labels are clinically acceptable. The SmPCs are consistent with those for the originator products. The PIL is 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 not submitting a risk management plan for these products.

Conclusion
The grant of Marketing Authorisations is recommended.
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, PIL and labelling are acceptable. The SmPCs are consistent with those for the reference products. The PIL is 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 equivalents of the reference products, Ikorel 10 mg and 20 mg Tablets (Sanofi-Aventis France). 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

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