Public Assessment Report

Decentralised Procedure

Nicorandil 10 mg Tablets
Nicorandil 20 mg Tablets

Procedure Nos: UK/H/2768/001-2/DC

UK Licence Nos: PL 18585/0028-9

Billev Pharma ApS
LAY SUMMARY

On 22 December 2010, Portugal and the UK agreed to grant Marketing Authorisations to Billev Pharma ApS for the medicinal products Nicorandil 10 mg and 20 mg Tablets (PL 18585/0028-9; UK/H/2768/001-2/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 18 January 2011.

These are prescription-only medicines (POM) used to treat angina. Angina is a chest pain that occurs when the heart muscle does not receive enough blood to supply it with oxygen when it is working hard. Angina can be brought on by physical activity, sudden cold or stress.

The active ingredient nicorandil belongs to a group of medicines called vasodilators. Nicorandil relieves angina by widening the blood vessels that supply the heart muscle to increase the blood supply. Nicorandil also opens up blood vessels elsewhere in the body to reduce the amount of work the heart has to do to pump blood around the body.

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; hence Marketing Authorisations were granted.
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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 |
| **Type of Application** | Generic, Article 10.1     |
| **Active Substance**    | Nicorandil               |
| **Form**                | Tablets                  |
| **Strength**            | 10 mg and 20g            |
| **MA Holder**           | Billev Pharma ApS        |
|                         | Fuglebækgaard, Elmsgårdsvej 1A, |
|                         | Torslev, 3630 Jaegerspris, Denmark |
| **Reference Member State (RMS)** | UK               |
| **Concerned Member State (CMS)** | Portugal |
| **Procedure Numbers**   | UK/H/2768/001-2/DC       |
| **Timetable**           | Day 210 – 22 December 2010 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Nicorandil 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10mg of nicorandil.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.
Tablets are white, round, scored on one side and embossed on the other side with ’10’. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

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

4.2 Posology and method of administration
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: There is no special requirement for dosage reduction in elderly patients. As with all medicines, the lowest effective dosage should be used.
Children: A paediatric dosage has not been established and use of nicorandil is not recommended.

4.3 Contraindications
Hypersensitivity to the nicorandil or to any of the excipients.
Nicorandil is contraindicated in patients with cardiogenic shock, left ventricular failure with low filling pressures and in hypotension. It is also contraindicated in patients who have demonstrated an idiosyncratic response. Due to the risk of severe hypotension, the concomitant use of nicorandil and phosphodiesterase 5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) is contraindicated.

4.4 Special warnings and precautions for use
The use of nicorandil should be avoided in patients with depleted blood volume, low systolic blood pressure, acute pulmonary oedema or acute myocardial infarction with acute left ventricular failure and low filling pressures.
Therapeutic doses of nicorandil may lower the blood pressure of hypertensive patients and therefore nicorandil, as with other antianginal agents, should be used with care when prescribed with antihypertensive drugs.
Gastrointestinal ulceration, skin ulceration, and ulcers of the mucosal membranes have been reported with nicorandil (see Section 4.8). These tend to be refractory to treatment and most only respond to withdrawal of nicorandil treatment.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

4.6 Pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common ($\geq 1/10$)</td>
<td>Angioedema</td>
</tr>
<tr>
<td>Common ($1/100$ to $&lt;1/10$)</td>
<td>Headache, usually of a transitory nature, especially when treatment is initiated.</td>
</tr>
<tr>
<td>Uncommon ($1/1,000$ to $&lt;1/100$)</td>
<td>Dizziness.</td>
</tr>
<tr>
<td>Rare ($1/10,000$ to $&lt;1/1,000$)</td>
<td>Nausea and vomiting.</td>
</tr>
<tr>
<td>Very rare ($&lt;1/10,000$)</td>
<td>Hypertension at high therapeutic doses.</td>
</tr>
<tr>
<td>Not known (cannot be estimated from the available data)</td>
<td>Nausea and vomiting.</td>
</tr>
</tbody>
</table>

Immune system disorders

Nervous system disorders

Cardiac disorders

Uncommon: An increase in heart rate at high doses.

Vascular disorders

Uncommon: Hypotension at high therapeutic doses.

Gastrointestinal disorders

Common: Nausea and vomiting.

Rare: Persistent aphirosis or mouth ulcers which were occasionally severe.

Very rare: Gastrointestinal ulcerations, such as small intestine ulcer, large intestine ulcer, and anal ulcerations and rectal bleeding. These ulcers may develop into perforation, fistulating disease, or abscess formation (see Sections 4.4 and 4.5).

Hepato-biliary disorders

Rare: Hepatic function abnormalities.
Skin and subcutaneous tissue disorders
Rare: Various types of rash.

Musculoskeletal & connective tissue disorders
Rare: Myalgia.

General disorders and administration site conditions
Common: A feeling of weakness.

The following additional adverse reactions have been reported during postmarketing experience; they are derived from spontaneous reports, and therefore the frequency of these adverse reactions is not known:

Skin and subcutaneous tissue disorders
Skin and mucosal ulcerations (mainly peri-anal, genital, and para-stomal ulcerations).

Other Clinical Trials – IONA (Impact of Nicorandil in Angina).
In addition, the following undesirable effects occurred at a different frequency in the IONA trial which was a study of subjects at high risk of cardiovascular events.

Gastrointestinal disorders
Common: rectal bleeding.
Uncommon: Cases of gastritis and oesophagitis were noted in the IONA study, but the difference in incidence between the nicorandil group and the placebo group was not statistically significant.
Uncommon: mouth ulcers.
Very Rare: abdominal pain.

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

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

Immune system disorders
Uncommon: angioedema.

Musculoskeletal & connective tissue disorders
Uncommon: myalgia.

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

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Other vasodilators used in cardiac diseases
ATC code: C01DX16

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

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

The study was a randomised, double blind, placebo controlled, cardiovascular endpoint study carried out in 5126 patients to determine if Nicorandil could reduce the frequency of coronary events in men
and women with chronic stable angina and standard anti anginal treatment at high risk of cardiovascular events defined by either: 1) previous myocardial infarction, or 2) coronary artery bypass grafting, or 3) coronary artery disease confirmed by angiography, or a positive exercise test in the previous two years, together with one of the following: left ventricular hypertrophy on the ECG, left ventricular ejection fraction ≤ 45%, or an end diastolic dimension of > 55 mm, age ≤ 65, diabetes (either type 1 or type 2), hypertension, peripheral vascular disease, or cerebrovascular disease. Patients were excluded from the study if they were receiving a sulphonylurea as it was felt these patients may not benefit; (sulphonylurea agents have the potential to close potassium channels and may thus antagonise some of the effects of nicorandil). Study follow up for endpoint analysis was between 12 and 36 months with a mean of 1.6 years.

The primary endpoint of coronary heart disease (CHD) death, non-fatal myocardial infarction, or unplanned hospital admission for cardiac chest pain, occurred in 13.1% of patients treated with nicorandil compared with 15.5% of patients receiving placebo (hazard ratio 0.83, p=0.014). The rate of acute coronary syndrome (CHD death, non fatal MI or unstable angina) was 6.1% in patients treated with nicorandil compared with 7.6% in patients receiving placebo (hazard ratio 0.79, p=0.028). All cardiovascular events were significantly less in the nicorandil than placebo group 14.7% vs 17.0% (hazard ratio 0.86, p=0.027). The validity of these findings was confirmed by re-analysing the primary endpoint using all cause rather than cardiovascular mortality (nicorandil 14.9% compared with placebo 17.3%, hazard ratio 0.85, p=0.021). The study was not expressly powered to, nor did it detect any statistically significant reduction in any individual component endpoints.

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

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

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

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Maize starch
croscarmellose sodium
stearic acid
mannitol.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
18 months.

Each blister should be used within 30 days of opening.

6.4 Special precautions for storage
Store below 25°C. Store in the original package in order to protect from moisture.

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

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.
7 MARKETING AUTHORISATION HOLDER
Billev Pharma ApS
Fuglebækgaard, Elmegårdsvej 1A
Tørslev
3630 Jægerspris
Denmark

8 MARKETING AUTHORISATION NUMBER(S)
PL 18585/0028

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/01/2011

10 DATE OF REVISION OF THE TEXT
18/01/2011
1 NAME OF THE MEDICINAL PRODUCT
Nicorandil 20mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 20mg of nicorandil.

For a full list of excipients see Section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

Tablets are white, round, scored on one side and embossed on the other side with '20'.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

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

4.2 Posology and method of administration
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: There is no special requirement for dosage reduction in elderly patients. As with all
medicines, the lowest effective dosage should be used.

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

4.3 Contraindications
Hypersensitivity to the nicorandil or to any of the excipients.

Nicorandil is contraindicated in patients with cardiogenic shock, left ventricular failure with low filling
pressures and in hypotension. It is also contraindicated in patients who have demonstrated an
idiosyncratic response. Due to the risk of severe hypotension, the concomitant use of nicorandil and
phosphodiesterase 5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) is contraindicated.

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Therapeutic doses of nicorandil may lower the blood pressure of hypertensive patients and therefore
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antihypertensive drugs.

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

Very common (≥1/10);
Common (≥1/100 to <1/10);
Uncommon (≥1/1,000 to <1/100);
Rare (≥1/10,000 to <1/1,000);
Very rare (<1/10,000),
Not known (cannot be estimated from the available data)

Immune system disorders
Very rare: Angioedema.

Nervous system disorders
Very common: Headache, usually of a transitory nature, especially when treatment is initiated.
Common: Dizziness.

Cardiac disorders
Uncommon: An increase in heart rate at high doses.

Vascular disorders
Common: Cutaneous vasodilation with flushing.
Uncommon: Hypotension at high therapeutic doses.

Gastrointestinal disorders
Common: Nausea and vomiting.
Rare: Persistent aphthosis or mouth ulcers which were occasionally severe.
Very rare: Gastrointestinal ulcerations, such as small intestine ulcer, large intestine ulcer, and anal ulcerations and rectal bleeding. These ulcers may develop into perforation, fistulating disease, or abscess formation (see Sections 4.4 and 4.5).

Hepato-biliary disorders
Rare: Hepatic function abnormalities.

Skin and subcutaneous tissue disorders
Rare: Various types of rash.
Musculoskeletal & connective tissue disorders
Rare: Myalgia.

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ventricular ejection fraction \( \leq 45\% \), or an end diastolic dimension of > 55 mm, age \( \leq 65 \), 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.

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

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

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Maize starch
croscarmellose sodium
stearic acid
mannitol.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
18 months.

Each blister should be used within 30 days of opening.

6.4 Special precautions for storage
Store below 25°C. Store in the original package in order to protect from moisture.

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

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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8 MARKETING AUTHORISATION NUMBER(S)
PL 18585/0029

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/01/2011

10 DATE OF REVISION OF THE TEXT
18/01/2011
Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Noricandil 10mg Tablets
Noricandil 20mg Tablets
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, 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

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

2. BEFORE YOU TAKE NORICANDIL

Do not take Noricandil:
- If you are allergic (hypersensitive) to noricandil or any of the other ingredients in this medicine. (See section 6 of this leaflet for a list of ingredients).
- If you have any heart conditions such as a low blood output from the heart or if you have suffered from heart failure.
- If you have low blood pressure.
- If you are using medicines for treating impotence such as sildenafil, tadalafil and vardenafil.

Take special care with Noricandil
Tell your doctor before you take Noricandil if you:
- have severe mouth ulcerations.
- are taking medicines to treat high blood pressure.

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

Taking/using other medicines:
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Noricandil can affect the way some other medicines work and some medicines can affect the way noricandil works.

Please tell your doctor if you are taking or have recently taken:
- medicines for blood pressure or angina that work on blood vessels such as hydralazine and minoxidil
- antidepressants such as amitryptiline, doxepin and imipramine
- alcohol
- medicines used to treat impotence such as sildenafil, tadalafil and vardenafil
- medicines for inflammation (corticosteroids such as prednisolone)

Taking Noricandil with food and drink:
Do not drink alcohol while you are taking this medicine.

Pregnancy and breast-feeding:
Ask your doctor or pharmacist for advice before taking any medicine.
If you are pregnant or think you might be pregnant you should not use Noricandil.
If you are breast-feeding you should not use Noricandil.

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

3. HOW TO TAKE NORICANDIL

Always take Noricandil exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. You should continue to take your Noricandil as long as your doctor tells you to.
Tablets should be swallowed with a glass of water at the same time each day.

Adults and the elderly:
Your doctor will usually start your treatment with a dose of 10 mg twice daily, to be taken in the morning and evening.
Your doctor may increase this dose if necessary. The usual maximum dose is 30 mg twice daily.
The same doses can be used in patients that are older than 70 years of age.

If you take more Noricandil than you should:
If you take more Noricandil tablets than you should contact your doctor or the nearest hospital emergency department. Symptoms of overdose are you may feel dizzy or weak or have difficulty breathing or experience wheezing.
If you forget to take a Nicorandil:
Do not worry if you have missed a dose. Take your next dose at the right time and then carry on as before. Do not take a double dose next time to make up for a forgotten dose.

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

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Nicorandil can cause side effects, although not everybody gets them. If you experience the following, stop taking this medicine and tell your doctor immediately or go to the casualty department of your nearest hospital:

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

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

The following side effects may also occur:

**Very Common (affecting more than 1 in every 10 people)**
- Headaches – these may occur in the first few days of treatment, but should disappear with time. If not, talk to your doctor.

**Common (affecting up to 1 in 10 people)**
- Feeling sick or vomiting
- Weakness or dizziness
- Flushing

**Uncommon (affecting more than 1 in 1,000 patients but less than 1 in 100 patients)**
- An increase in heart rate when taking high doses
- Low blood pressure when taking high doses

**Rare (affecting more than 1 in 10,000 patients but less than 1 in 1,000)**
- Muscle pain
- Rashes
- Persistent mouth ulcers
- Yellowing of the skin

**Very Rare (affecting fewer than 1 in 10,000 patients)**
- Swelling of the skin similar to hives
- Ulcers including ulcers and bleeding of the back passage

If you experience any of the following tell your doctor immediately:
- Palpitations – sensations of fast or irregular heartbeat
- Ulcers or pain of the back passage
- Bleeding or discharge of pus from the back passage or abnormal vaginal discharge
- Swelling, tenderness, irritation and itching on the skin around the back passage
- Vomiting blood, severe or lasting stomach pains or dark, tarry stools
- Swelling of the lips and tongue.

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

5. HOW TO STORE NICORANDIL

Keep out of the reach and sight of children.

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

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

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

Use the blister within 30 days of opening.

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

6. FURTHER INFORMATION

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

What Nicorandil looks like and contents of the pack:
Nicorandil 10 mg tablets are white, round, scored on one side and embossed with “10” on the other side.
Nicorandil 20 mg tablets are white, round, scored on one side and embossed with “20” on the other side.
Nicorandil is available in blister packs. Each blister contains 10 tablets. The blisters are packed in cartons of 60 tablets.

Marketing Authorisation Holder and Manufacturer:

Marketing Authorisation Holder
Billev Pharma ApS, Fuglebakgaard, Eimegårdsvej 1A, Tæslev, 3630 Jægerspris, Denmark

Manufacturer
Laboratories BTT, Z.I. de Krafft, 67 150 ERSTEIN, France

Distributed by:
Genus Pharmaceuticals
Park View House, 65 London Road, Newbury, Berkshire RG14 1JN, UK

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

This leaflet was approved in December 2010

1145
Module 4

Each tablet contains 10 mg nicorandil. 60 tablets

For oral use. Read the package leaflet before use.
Keep out of the reach and sight of children.
Store below 25°C.
Store in the original package to protect from moisture.
Use each blister strip within 30 days of opening.
Each tablet contains 20 mg ncorandil.

60 tablets
Module 5
Scientific discussion during initial procedure

1 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 18585/0028-9; UK/H/2768/001-2/DC) could be approved. The products are prescription-only medicines (POM) used in the:
- Prevention and long-term treatment of chronic stable angina pectoris
- Reduction in the risk of acute coronary syndromes in patients with chronic stable angina and at least one of the following risk factors:
  - previous myocardial infarction (MI)
  - previous coronary artery bypass graft (CABG)
  - coronary heart disease (CHD) on angiography or a positive exercise test together with one of the following: left ventricular hypertrophy (LVH) on electrocardiogram (ECG), left ventricular dysfunction, Age ≥ 65, diabetes mellitus (type I or II excluding those on sulphonylureas, see section 5.1 of the Summary of Product Characteristics), hypertension or documented vascular disease

These applications were submitted under Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Ikorel 10 mg and 20mg Tablets (Sanofi-Aventis, France), which were first licensed in the EU on 12 August 1992. The corresponding reference products in the UK are Ikorel 10mg and 20mg Tablets (Aventis Pharma Limited, UK), which were first authorised in the UK on 6 June 1994.

Nicorandil is a nicotinamide ester with potassium channel opener. 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 poststenotic regions and the oxygen balance in the myocardium.

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.

Two single-dose, bioequivalence studies were submitted to support these applications, comparing the test products Nicorandil 10 mg and 20 mg Tablets (Billev Pharma ApS, Denmark) and the reference products Ikorel 10 mg and 20 mg Tablets (Sanofi-Aventis, France).

With the exception of the bioequivalence studies, no new clinical data were 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. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).
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.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Nicorandil 10 mg and 20 mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Nicorandil 10 mg Tablets  
| | Nicorandil 20 mg Tablets |
| Name of the active substance (INN) | Nicorandil |
| Pharmacotherapeutic classification (ATC code) | Other vasodilators used in cardiac diseases (C01DX16) |
| Pharmaceutical form and strength | Tablets  
| | 10 mg and 20 mg |
| Reference numbers for the Decentralised Procedure | UK/H/2768/001-2/DC |
| Reference Member State (RMS) | United Kingdom |
| Concerned Member States (CMS) | Portugal |
| Marketing Authorisation Numbers | PL 18585/0028-9 |
| Name and address of the authorisation holder | Billev Pharma ApS  
| | Fuglebækgaard, Elmsgårdsvej 1A,  
| | Torslev, 3630 Jaegerspris, Denmark |
III     SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS
ACTIVE SUBSTANCE
INN: Nicorandil
Chemical Name: N-[2-(Nitro-oxy)ethyl]-3-pyridine carboxamide
Molecular Formula: C₈H₉N₃O₄
Structure:

Molecular weight: 211.18 g/mol
Appearance: A white to light cream, crystalline powder. Slightly soluble in water, methanol and ethanol

At the time of the assessment of these applications, nicorandil was not the subject of a 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.

Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the specification limits. Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for all working standards.

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.

DRUG PRODUCT
Other Ingredients
Other ingredients consist of the pharmaceutical excipients, namely maize starch, croscarmellose sodium, stearic acid and mannitol. Appropriate justifications for the inclusion of each excipient have been provided.

All excipients comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, stable products that could be considered generic medicinal products of the reference products Ikorel 10 mg and 20mg tablets (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 pilot-scale batches, the manufacturing process has been validated and has shown satisfactory results. The Marketing Authorisation Holder has committed to submitting validation data performed on full-scale batches as soon as they are available.

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

Container Closure System
The tablets are packaged in aluminium/aluminium blisters of 10 tablets. In each blister each tablet is linked to a molecular sieve desiccant. The blisters are packed in cartons of 60 tablets.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations (Directive 2002/72/EC, as amended) concerning materials in contact with foodstuff.

Stability
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. Based on the results, a shelf-life of 18 months has been proposed for the products in the unopened blister; with a shelf-life of 30 days once the blisters are opened. The storage instructions are “Store below 25°C. Store in the original package in order to protect from moisture.”

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence studies.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are pharmaceutically satisfactory.
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 it contains.

**MAA Forms**
All aspects of the MAA forms are pharmaceutically satisfactory.

**Expert Report**
The pharmaceutical expert report is 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 are well-known, no further non-clinical studies are required and none have been provided.

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

ENVIRONMENTAL RISK ASSESSMENT
A suitable justification has been provided for non-submission of an Environmental Risk Assessment. As these products are intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of Marketing Authorisations is recommended.
III.3 CLINICAL ASPECTS
CLINICAL PHARMACOLOGY
The clinical pharmacology of nicorandil is well-known. With the exception of the below bioequivalence studies, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

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

Study 1
A randomised, single-dose, open-label, two-treatment, two-sequence, two-period, two-way crossover study comparing the pharmacokinetics of the test product Nicorandil 10 mg Tablets (Billev Pharma ApS, Denmark) and the reference product Ikorel 10 mg Tablets (Sanofi-Aventis, France) in healthy male and female adult subjects under fasting conditions

The subjects were given a single dose of either treatment with 240 ml of water after at least a 10-hour overnight fast. Blood samples were collected before and up to 10 hours after each administration. The washout period between the treatment arms was 7 days. The pharmacokinetic results (presented as arithmetic means, ratios and 90% confidence intervals) are presented below:

Pharmacokinetic parameters (arithmetic means ± standard deviations, ratio and confidence intervals [CI]) of nicorandil

<table>
<thead>
<tr>
<th></th>
<th>Nicorandil 10 mg Tablets (Test)</th>
<th>Ikorel 10 mg Tablets (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-t} (ng h/mL)</td>
<td>241.26±56.90</td>
<td>254.15±52.87</td>
<td>94.50</td>
<td>89.15-100.18</td>
</tr>
<tr>
<td>AUC_{0-inf} (ng h/mL)</td>
<td>242.77±56.88</td>
<td>255.74±52.46</td>
<td>94.48</td>
<td>89.19-100.08</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>173.59±47.09</td>
<td>201.01±79.99</td>
<td>89.76</td>
<td>80.17-100.48</td>
</tr>
</tbody>
</table>

AUC_{0-t}: area under the plasma concentration-time curve from time zero to t hours
AUC_{0-inf}: area under the plasma concentration-time curve from time zero to infinity
C_{max}: maximum plasma concentration
Ratios and 90% geometric CI calculated from ln-transformed data

The current Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) defines the confidence limits as 80% to 125% for C_{max} and AUC values. The 90% confidence intervals of the test/reference ratio of geometric means for AUC_{0-t}, AUC_{0-inf} and C_{max} lie within the acceptable limits. Thus, the data support the claim that the test product Nicorandil 10 mg Tablets (Billev Pharma ApS, Denmark) is bioequivalent to the reference product Ikorel 10 mg Tablets (Sanofi-Aventis, France).
Study 2
A randomised single-dose, open-label, two-treatment, two-period, two sequence, crossover comparing the pharmacokinetics of the test product Nicorandil 20 mg tablet (Billev Pharma ApS, Denmark) and the reference product Ikorel 20 mg Tablets (Sanofi-Aventis, France) in healthy adult male subjects under fasting conditions.

The subjects were given a single dose of either treatment with 240 ml of water after at least a 10-hour overnight fast. Blood samples were collected before and up to 8 hours after each administration. The washout period between the treatment arms was 7 days. The pharmacokinetic results (presented as arithmetic means, ratios and 90% confidence intervals) are presented below:

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters (arithmetic means ± standard deviations, ratios and confidence intervals [CI]) of nicorandil</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>AUC_{0-4} (ng h/ml)</td>
<td>586.80±127.93</td>
<td>574.59±146.86</td>
<td>103.05</td>
<td>97.75-108.65</td>
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<tr>
<td>AUC_{0-inf} (ng h/mL)</td>
<td>598.07±129.52</td>
<td>583.96±147.70</td>
<td>103.26</td>
<td>98.06-108.74</td>
</tr>
<tr>
<td>C_{max} (ng/ml)</td>
<td>367.94±122.93</td>
<td>358.31±159.70</td>
<td>105.83</td>
<td>94.79-118.15</td>
</tr>
</tbody>
</table>

AUC_{0-4} area under the plasma concentration-time curve from time zero to 4 hours
AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
Ratios and 90% geometric CI calculated from ln-transformed data

The current Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) defines the confidence limits as 80% to 125% for C_{max} and AUC values. The 90% confidence intervals of the test/reference ratio of geometric means for AUC_{0-4}, AUC_{0-inf} and C_{max} lie within the acceptable limits. Thus, the data support the claim that the test product Nicorandil 20 mg Tablets (Billev Pharma ApS, Denmark) is bioequivalent to the reference product Ikorel 20 mg Tablets (Sanofi-Aventis, France).

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 data generated during the bioequivalence studies, no new safety data were submitted and none are required for these types of applications. No new or unexpected safety issues were raised by the bioequivalence data.

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.

A suitable justification has been provided for not submitting a risk management plan for these products.
SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPCs, PIL and labelling are clinically 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.

CLINICAL EXPERT REPORT
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossiers.

CONCLUSION
The grant of Marketing Authorisations is recommended.
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 studies, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s 10 mg and 20 mg strength tablets and their respective reference products.

SAFETY
With the exception of the safety data from the bioequivalence studies, no new data were submitted and none are required for applications of this type. As the safety profile of nicorandil is well-known, no additional data were required. No new or unexpected safety concerns were raised from the bioequivalence studies.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory, and consistent with those for the reference products, where appropriate, along with current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. 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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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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