Annex III

Summary of product characteristics, labelling and package leaflet

Note:

This Summary of Product Characteristics, labelling and package leaflet is the outcome of the referral procedure to which this Commission decision relates.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ikorel and associated names (see Annex I) 10 mg tablets
Dancor and associated names (see Annex I) 10 mg tablets
Ikorel and associated names (see Annex I) 20 mg tablets]
Dancor and associated names (see Annex I) 20 mg tablets
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITAVE COMPOSITION

[To be completed nationally]

3. PHARMACEUTICAL FORM

[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<Invented name> is indicated in adults for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or have a contraindication or intolerance to first-line antianginal therapies (such as beta-blockers and/or calcium antagonists*)*.

4.2 Posology and method of administration

Posology
The usual therapeutic range is 10 to 20 mg twice daily. The usual starting dose is 10 mg twice daily (bid), in the morning and in the evening preferably. It is recommended that the dose be titrated upwards in accordance with the patient's needs, response and tolerance up to 40 mg twice daily, if necessary. A lower starting dose of 5 mg twice daily may be used in patients particularly prone to headache.

Elderly
There are no special dose requirements for elderly patients, but as with all medicines, use of the lowest effective dose is recommended.

Patients with liver and/or renal impairment
There are no special dosage requirements for patients with liver and/or renal impairment.

Paediatric population
<Invented name> is not recommended in paediatric patients since its safety and efficacy have not been established in this patient group.

Method of administration
<Invented name> is administered by oral route.
The tablets are to be swallowed in the morning and in the evening as a whole with some liquid. Administration is independent from food intake.

4.3 Contraindications

- Hypersensitivity to nicorandil or to any of the excipients listed in section 6.1
- Patients with shock (including cardiogenic shock), severe hypotension, or left ventricular dysfunction with low filling pressure or cardiac decompensation
- Use of phosphodiesterase 5 inhibitors, since this can lead to a serious drop in blood pressure (see section 4.5)
- Use of soluble guanylate cyclase stimulator(s) (such as riociguat) since it can lead to a serious fall in blood pressure (see section 4.5)
- Hypovolaemia
- Acute pulmonary oedema

4.4 Special warnings and precautions for use

Ulcerations
Gastrointestinal ulcerations, skin and mucosal ulcerations have been reported with nicorandil (see section 4.8).

- *Gastrointestinal ulcerations*

Nicorandil induced ulceration may occur at different locations in the same patient. They are refractory to treatment and most only respond to withdrawal of nicorandil treatment. If ulceration(s) develops, nicorandil should be permanently discontinued (see section 4.8). Healthcare professionals should be aware of the importance of a timely diagnosis of nicorandil-induced ulcerations and of a rapid withdrawal of nicorandil treatment in case of occurrence of such ulcerations. Based on available information, the time between starting nicorandil use and the onset of ulceration ranges from shortly after initiating nicorandil treatment to several years after starting nicorandil.

Gastrointestinal haemorrhage secondary to gastrointestinal ulceration has been reported with nicorandil. Patients taking acetylsalicylic acid or NSAIDs (Non Steroid Anti Inflammatory Drugs) concomitantly are at increased risk for severe complications such as gastrointestinal haemorrhage. Therefore caution is advised when concomitant use of acetylsalicylic acid or NSAIDs and nicorandil is considered (see section 4.5).

If advanced, ulcers may develop into perforation, fistula, or abscess formation. Patients with diverticular disease may be at particular risk of fistula formation or bowel perforation during nicorandil treatment.

Gastrointestinal perforations in context of concomitant use of nicorandil and corticosteroids have been reported. Therefore, caution is advised when concomitant use of corticosteroids is considered.

- *Eye ulcerations*

Very rare conjunctivitis, conjunctival ulcer and corneal ulcer have been reported with nicorandil. Patients should be advised of the signs and symptoms and monitored closely for corneal ulcerations. If ulceration(s) develops, nicorandil should be discontinued (see section 4.8).

Decrease of blood-pressure
Caution is advised if nicorandil is used in combination with other medicinal products with blood pressure lowering effect (see section 4.5 and 4.8).

Heart failure
Due to lack of data, caution is advised to use nicorandil in patients with heart failure class NHYA III or IV.

Hyperkalaemia

Severe hyperkalaemia has been very rarely reported with nicorandil. Nicorandil should be used with care in combination with other medical products that may increase potassium levels, especially in patients with moderate to severe renal impairment (see sections 4.5 and 4.8).

Desiccant
The tablets are sensitive to moisture; hence the patients should be advised to keep the tablets in their blister until intake. Besides the nicorandil tablets, each blister contains active substance-free silica gel tablets as desiccant in a separate blister segment which is marked accordingly. The patients should be advised not to take these tablets. Although any accidental intake of this desiccant is usually harmless, it may alter the scheduled intake of the active tablets.

Paediatric population
<Invented name> is not recommended in paediatric patients since its safety and efficacy have not been established in this patient group.

G6PD deficiency
<Invented name> should be used with caution in patients with glucose-6-phosphate-dehydrogenase deficiency. Nicorandil acts in parts through its organic nitrate moiety. The metabolism of organic nitrates can result in the formation of nitrites which may trigger methemoglobinemia in patients with glucose-6-phosphate dehydrogenase deficiency.

4.5 Interaction with other medicinal products and other forms of interaction

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 (synergic effect).
Concomitant use of soluble guanylate cyclase stimulator (such as riociguat) is contraindicated, since it can lead to a serious drop in blood pressure.

Therapeutic doses of nicorandil may lower the blood pressure.
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.

Dapoxetine should be prescribed with caution in patients taking nicorandil due to possible reduced orthostatic tolerance.

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

In patients concomitantly receiving NSAIDs including acetylsalicylic acid for both cardiovascular prevention and anti-inflammatory doses, there is an increased risk for severe complications such as gastrointestinal ulceration, perforation and haemorrhage (see section 4.4).

Caution is advised when nicorandil is used in combination with other medical products that may increase potassium levels (see sections 4.4 and 4.8).

The metabolism of nicorandil is not significantly affected by cimetidine (a CYP inhibitor), or rifampicin (a CYP3A4 inducer). Nicorandil does not affect the pharmacodynamics of acenocoumarol.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of nicorandil in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure**,** it is preferable to avoid the use of <Invented name> during pregnancy.

Breast-feeding
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 <Invented name> is not recommended during breastfeeding.

Fertility
There are insufficient data on fertility to estimate the risk for humans (see section 5.3).

4.7 Effects on ability to drive and use machines

<Invented name> has an influence on the ability to drive and use machines. Indeed, as with other vasodilators, blood pressure-lowering effects as well as dizziness and feeling weakness induced by nicorandil can reduce the ability to drive or to use machines. This effect can be increased in conjunction with alcohol or other medicinal products with blood pressure lowering effect (e.g. vasodilators, tricyclic antidepressants) (see section 4.5). Therefore, patients should be advised not to drive or use machines if these symptoms occur.

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reaction reported in clinical trials is headache occurring in more than 30% of patients, particularly in the first days of treatment and responsible of most of study withdrawal. Progressive dose titration may reduce the frequency of these headaches (see section 4.2).

In addition, serious adverse reactions including ulcerations and their complications (see section 4.4) were reported during the post marketing surveillance of nicorandil.

Tabulated list of adverse reactions
The frequencies of adverse reactions reported with nicorandil are summarised in the following table by system organ class (in MedDRA) and by frequency. Frequencies are defined as: 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), Not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Metabolism and nutrition disorders					Hyperkalaemia (see section 4.4 and 4.5)	
Nervous system disorders	Headache	Dizziness				
Eye disorders					Corneal ulcer, conjunctival ulcer, conjunctivitis (see section 4.4)	Diplopia
Cardiac disorders		Heart rate increased				

	Very common	Common	Uncommon	Rare	Very rare	Not known
Vascular disorders		Cutaneous vasodilation with flushing	Decrease in blood pressure (see section 4.4)			
Gastroinstestinal disorders		Vomiting, nausea		Gastrointestinal ulcerations (stomatitis, aphtosis, mouth ulcer, tongue ulcer, small intestinal ulcer, large intestinal ulcer, anal ulcer) (see below and section 4.4)		Gastrointestinal haemorrhage (see section 4.4)
Hepatobiliary disorders					Liver disorders such as hepatitis, cholestasis, or jaundice	
Skin and subcutaneous tissue disorders				Rash, pruritus	Angioedema, Skin and mucosal ulcerations (mainly peri-anal ulcerations, genital ulcerations and parastomal ulcerations) (see section 4.4)	
Musculoskeletal and connective tissue disorders				Myalgia		
General disorders and administration site conditions		Feeling of weakness				

Description of selected adverse reactions

Gastrointestinal ulcerations

Complications of gastrointestinal ulceration such as perforation, fistula, or abscess formation sometimes leading to gastrointestinal haemorrhage and weight loss have been reported (see section 4.4).

Additional information

In addition, the following adverse reactions have been reported with different frequencies in the IONA (Impact of Nicorandil in Angina) study, where nicorandil has been used on top of standard therapy in patients with stable angina and at high risk of cardiovascular events (see section 5.1).

	Common	Uncommon	Very rare

	Common	Uncommon	Very rare
Gastroinstestinal disorders	Rectal bleeding	Mouth ulcer	Abdominal pain
Skin and subcutaneous tissue disorders		Angioedema	
Musculoskeletal and connective tissue disorders		Myalgia	

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
In case of acute overdose, the likely symptomatology may be peripheral vasodilation with a fall in blood pressure and reflex tachycardia.

Management
Monitoring of cardiac function and general supportive measures are recommended. If not successful, increase in circulating plasma volume by substitution of fluid is recommended. In life-threatening situations, administration of vasopressors must be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other vasodilators used in cardiac diseases, ATC code: C01DX16

Mechanism of action
Nicorandil, a nicotinamide ester, is a vasodilator agent with a dual mechanism of action, which leads to relaxation of smooth tonic vascular muscles in both venous and arterial part of vessels.

It possesses a potassium-channel opening effect. This activation of potassium channels induces vascular cell membrane hyperpolarisation with an arterial muscle relaxant effect, thereby leading to arterial dilatation and afterload reduction. In addition, the activation of the potassium channel leads to cardioprotective effects mimicking ischemic pre-conditioning.

Due to its nitrate moiety, nicorandil relaxes also vascular smooth muscle, particularly in the venous system via an increase in intracellular cyclic guanosine monophosphate (cGMP). This results in an increased pooling in capacitance vessels with a decrease in preload.

Pharmacodynamic effects
Nicorandil has been shown to exert a direct effect on the coronary arteries, both on normal and stenotic segments, without leading to a steal phenomenon. Furthermore, the reduction of end-diastolic pressure and wall tension decreases the extravascular component of vascular resistance. Ultimately, this results in an improved oxygen balance in the myocardium and improved blood flow in the post-stenotic areas of the myocardium.

Furthermore, nicorandil has demonstrated a spasmolytic activity in both in vitro and in vivo studies and reverses coronary spasm induced by methacholine or noradrenalin.

Nicorandil has no direct effect on myocardial contractility.

Clinical efficacy and safety
The IONA study was a randomised, double blind, placebo controlled study carried out in 5126 patients more than 45 years old with chronic stable angina, treated with standard antianginal therapies and 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, 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 composite primary endpoint (coronary heart disease (CHD) death, non-fatal myocardial infarction, or unplanned hospital admission for cardiac chest pain), occurred in 337 patients (13.1%) of patients treated with nicorandil 20 mg twice daily compared with 389 patients (15.5%) of patients receiving placebo (hazard ratio 0.83; 95% confidence interval (CI) 0.72 to 0.97; p=0.014).

5.2 Pharmacokinetic properties

Nicorandil pharmacokinetics are linear from 5 mg to 40 mg.

Absorption
After oral administration, nicorandil is absorbed rapidly and completely from the gastrointestinal tract, independent from food intake. The absolute bioavailability is about 75%. There is no significant hepatic first pass effect. Maximum plasma concentrations (C_{max}) are reached after about 30- 60 minutes. The plasma concentration (and the area under the curve (AUC)) shows a linear proportionality to the dose.
Steady state is rapidly achieved (within 4 to 5 days) during repeated oral administration (bid regimen). At steady state, the accumulation ratio (based on AUC) is around 2 for 20 mg bid tablet and 1.7 for 10 mg bid tablet.

Distribution
Distribution of the product throughout the body remains stable, irrespective of dose, within the therapeutic range.
The volume of distribution of nicorandil after intravenous (iv) dosing is 1.04 L/kg of body weight. Nicorandil is only slightly bound to human plasma proteins (bound fraction estimated at about 25%).

Biotransformation
Nicorandil is principally metabolised in the liver by denitration in a series of compounds without cardiovascular activity. In plasma unchanged nicorandil accounted for 45.5% of the radioactive AUC and the alcohol metabolite, N-(2-hydroxyethyl)-nicotinamide for 40.5%. The other metabolites accounted for the remaining 20% of radioactive AUC.
Nicorandil is mainly eliminated in urine as metabolites since parent product is less than 1%, of the administered dose in human urines (0-48 hours). N-(2-hydroxyethyl)-nicotinamide is the most abundant metabolite (about 8.9% of the administered dose within 48 hours) followed by nicotinuric acid, (5.7%), nicotinamide (1.34%), N-methyl-nicotinamide (0.61%) and nicotinic acid (0.40%). These metabolites represented the major route of transformation of nicorandil.

Elimination
Decrease in plasma concentrations occurs in two phases:

- a rapid phase with a half-life of 1 hour approximately, representing 96% of the plasma exposure;

- a slow elimination phase occurring approximately 12 hours following 20 mg oral dose bid.

After 4-5 mg intravenous dosing (5 min infusion), the total body clearance was approximately 40-55 L/hour.
Nicorandil and its metabolites are mainly excreted by urinary route, faecal excretion being very low.

Special patient groups
No clinically relevant modifications of the nicorandil pharmacokinetic profile is evidenced in population at risk such as elderly people, liver disease patients and chronic renal failure patients.

Pharmacokinetic interactions
The metabolism of nicorandil appears not to be significantly modified by cimetidine or rifampicine, respectively an inhibitor and an inducer of liver microsomal mixed-function oxidases.

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 and carcinogenic potential.

Impairment of Fertility
Fertility studies showed no effects on mating ability in either male or female rats, but decreases in the number of live fetuses and implantation sites were noted at high doses. Histopathological changes of the testes (diminished spermatogenic cells) were determined in repeat dose toxicity studies. Additional investigative studies for testicular toxicity revealed decreased blood flow in the testis and decreased blood levels of testosterone. These results suggest that testicular toxicity by nicorandil is related to a sustained decrease in blood flow caused by reduction of cardiac output. Upon cessation of treatment, recovery from nicorandil-induced testicular toxicity was observed after 4 weeks; which indicates that the observed changes are reversible.

Embryotoxicity and peri- and post-natal toxicity
Radioactivity passed through the placenta in pregnant rats after administration of radioactively marked nicorandil.
Following exposure to nicorandil at doses that were maternally toxic, embryotoxicity was observed in the rat and rabbit. There was no evidence of teratogenicity (rat and rabbit), or abnormal pre- or post-natal physical or behavioural development (rat).

6. PHARMACEUTICAL PARTICULARS

[To be completed nationally]

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION: RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON for 10 mg and 20 mg

1. NAME OF THE MEDICINAL PRODUCT

Ikorel and associated names (see Annex I) 10 mg tablets
Dancor and associated names (see Annex I) 10 mg tablets
Ikorel and associated names (see Annex I) 20 mg tablets]
Dancor and associated names (see Annex I) 20 mg tablets
[See Annex I - To be completed nationally]
nicorandil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg nicorandil.
Each tablet contains 20 mg nicorandil.

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets
30 tablets
60 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains a drying agent in each blister strip.
Do not swallow drying agent.

8. EXPIRY DATE

EXP:
Use the strip within 30 days of opening.

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

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

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<Invented name> 10 mg [To be completed nationally]
<Invented name> 20 mg [To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister strip/ 10 mg and 20 mg

1. NAME OF THE MEDICINAL PRODUCT

Ikorel and associated names (see Annex I) 10 mg tablets
Dancor and associated names (see Annex I) 10 mg tablets
Ikorel and associated names (see Annex I) 20 mg tablets]
Dancor and associated names (see Annex I) 20 mg tablets
[See Annex I - To be completed nationally]

nicorandil

Oral use

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP:
Use the strip within 30 days of opening.

4. BATCH NUMBER

Lot:

5. OTHER

Do not swallow drying agent.

PACKAGE LEAFLET

Package leaflet: Information for the user

Ikorel and associated names (see Annex I) **10 mg tablets**
Dancor and associated names (see Annex I) **10 mg tablets**
Ikorel and associated names (see Annex I) **20 mg tablets]**
Dancor and associated names (see Annex I) **20 mg tablets**

[See Annex I - To be completed nationally]

nicorandil

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What <Invented name> is and what it is used for

<Invented name> contains a medicine called nicorandil. This belongs to a group of medicines called 'potassium channel activators'. It works by increasing the blood flow through the blood vessels of the heart. It improves the blood and oxygen supply of your heart muscle and reduces its workload.

<Invented name> is used to prevent or attenuate painful, straining symptoms (angina pectoris) of your heart disease. It is used in adult patients who do not tolerate or cannot take heart medicines called beta-blockers and/or calcium antagonists.

2. What you need to know before you take <Invented name>

Do not take <Invented name>:
- if you are allergic to nicorandil or any of the other ingredients of this medicine (listed in section 6).
- if you have low blood pressure (hypotension).
- if you have heart problems such as cardiogenic shock, or left ventricular failure with low filling pressure or cardiac decompensation or shock.
- if you are taking medicines to treat erectile dysfunction such as sildenafil, tadalfil, vardenafil (phosphodiesterase inhibitors) or medicines to treat pulmonary hypertension such as riociguat (guanylate cyclase stimulators). This may seriously affect your blood pressure.
- if you have a low blood volume.

- if you have a build-up of fluid in the lungs (pulmonary oedema).

Warnings and precautions
Talk to your doctor or pharmacist before taking <Invented name>.
Stop taking straight away nicorandil and talk to your doctor if you experience any of the following:
- Nicorandil may cause injuries to your gastrointestinal tract such as ulcers. This can develop problems such as bleeding, fistula, wholes, abscess, especially if you have diverticular disease (a digestive condition affecting the large intestine).
- If your eyes become red, itchy or swollen. You may have eye injuries, stop taking <Invented name> and contact your doctor immediately.

These side effects can occur at the beginning of treatment or latter in the treatment course. The only possible treatment is to stop nicorandil. Do not take aspirin or any medicines for inflammation (corticosteroids).

Talk to your doctor or pharmacist before taking <Invented name>:
- If you have a low blood pressure.
- If you have low blood potassium level and your doctor has prescribed potassium supplements, or if you are suffering from renal impairment or taking other medical products that may increase potassium levels.
- If you have heart problems such as heart failure.
- If you have glucose 6 Phosphate Deshydrogenase deficiency.

Children
- <Invented name> is not recommended in children.

Other medicines and <Invented name>
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because <Invented name> may affect the way some other medicines work. Also some medicines may affect the way <Invented name> works.

Do not take this medicine and talk to your doctor if you are taking the following:
- Medicine for impotence such as sildenafil, tadalafil or vardenafil.
- Medicines to treat pulmonary hypertension such as riociguat.

Tell your doctor, if you are taking any of the following:
- Medicines to treat high blood pressure.
- Medicines that widen the blood vessels.
- Medicines that increase blood potassium levels.
- Dapoxetine, a medicine used to treat premature ejaculation.
- Medicines for inflammation (corticosteroids, non-inflammatory steroidal drugs such as ibuprofen).
- Medicines for depression.
- Aspirin (acetylsalicylic acid).

<Invented name> with alcohol
Nicorandil may lower your blood pressure. If you drink alcohol while you are treated with <Invented name>, your blood pressure may be decreased even further.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
You should avoid taking this medicine while you are pregnant.

It is not known whether nicorandil passes in human milk. You should not breast-fed while you are taking this medicine.

Driving and using machines
<Invented name> may cause dizziness or weakness. If this happens, do not drive or use any tools or machines.

3. How to take <Invented name>

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is:
- The usual starting dose is 10 mg twice daily.
- In case you are particularly prone to headache, a lower dose of 5 mg twice daily might be prescribed by your doctor, for the first few days (2 to 7 days).
- Your doctor may increase the dose up to 20 mg twice daily depending on your needs, response to treatment and tolerance.

Preferably take one dose in the morning and one in the evening.
Swallow the tablet (oral use).
Do not take out or separate tablet from the blister strip until intake.

The tablet of 10 mg can be divided into equal doses.
For the tablet of 20 mg, the score line is only there to help you break the tablet if you have difficulty swallowing it whole.

Do not swallow the drying agent which is the bigger tablet on one end of each blister strip. It is included in the pack to protect <Invented name> tablets from moisture. On the blister, it is clearly indicated which tablet is the drying agent. If you do accidentally take any of these drying agent tablets, they should not harm you but you should straight away talk to your doctor.

If you take more <Invented name> than you should
If you take more tablets than you should, or if a child has swallowed any of your tablets, tell a doctor or go to a hospital casualty department straight away. Take the medicine pack with you. You may feel blood pressure lowering effect such as dizziness, feeling of weakness. You may also feel your heart is beating irregularly and faster.

If you forget to take <Invented name>
If you forget to take a dose, take it as soon as you remember, unless it is nearly time for your next dose.
Do not take a double dose to make up for a forgotten dose.

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

4. Possible side effects

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

Talk straight away to your doctor if you experience any of the following:
Nicorandil may cause injuries to your gastrointestinal tract such as ulcers in the mouth, tongue, stomach, guts (small and large), back passage. This can develop problems such as bleeding (blood in your stools or vomit), fistula (abnormal tube-like passage from one body cavity to another or to the

skin), wholes, abscess, weight loss. Ulcers can occur at other site such as: skin, genital tract and nasal passages or around a stoma (in those with an artificial opening for waste removal such as a colostomy or ileostomy).

Other side effects include:
Very common (may affect more than 1 in 10 people)
- Headache – This especially occurs during the first few days of treatment. Your doctor may progressively increase the dose to reduce the frequency of headaches.

Common (may affect up to 1 in 10 people)
- Dizziness
- Very fast, uneven or forceful heart-beat (palpitations)
- Flushing of the skin
- Feeling sick (nausea)
- Being sick (vomiting)
- Feeling of weakness.

Uncommon (may affect up to 1 in 100 people)
- Decrease in blood pressure.

Rare (may affect up to 1 in 1,000 people)
- Rash
- Itching
- Aching muscles not caused by exercise (myalgia).

Very rare (may affect up to 1 in 10,000 people)
- High potassium levels in the blood (hyperkalaemia)
- Red, itchy, swollen or watery eyes (conjunctivitis)
- Eye injuries
- Cornea injuries
- Yellowing of the skin and eyes, light coloured bowel motions, dark coloured urine – This may be signs of liver problems.
- Swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing
- Stomach aches.

Not known (frequency cannot be estimated from the available data)
- Double vision (diplopia).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store <Invented name>

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

[To be completed nationally]

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

[To be completed nationally]

Marketing Authorisation Holder and Manufacturer
[See Annex I - To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:
[See Annex I - To be completed nationally]

This leaflet was last revised in.
[To be completed nationally]

Other sources of information
Detailed information on this medicine is available on the website of {MS/Agency}