Annex I

List of the names, pharmaceutical form, strengths of the medicinal products, route of administration, Marketing Authorisation Holders in the Member States
<table>
<thead>
<tr>
<th>Member State (in EEA)</th>
<th>Marketing authorisation holder</th>
<th>Invented Name</th>
<th>Strength</th>
<th>Pharmaceutical form</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>MERCK Gesellschaft mbH Zimbagasse 5 1147 Wien Austria</td>
<td>Dancor 10 mg - Tabletten</td>
<td>10 mg</td>
<td>tablet</td>
<td>oral use</td>
</tr>
<tr>
<td>Austria</td>
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<td>Dancor 20 mg - Tabletten</td>
<td>20 mg</td>
<td>tablet</td>
<td>oral use</td>
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<td>Sanofi-Aventis Denmark A/S Slotsmarken 13 DK-2970 Hørsholm Denmark</td>
<td>ANGICOR</td>
<td>10 mg</td>
<td>tablet</td>
<td>oral use</td>
</tr>
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<td>ANGICOR</td>
<td>20 mg</td>
<td>tablet</td>
<td>oral use</td>
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<tr>
<td>France</td>
<td>Sanofi-Aventis France 1-13 boulevard Romain Rolland 75014 Paris France</td>
<td>IKOREL</td>
<td>10 mg</td>
<td>scored tablet</td>
<td>oral use</td>
</tr>
<tr>
<td>France</td>
<td>Sanofi-Aventis France 1-13 boulevard Romain Rolland 75014 Paris France</td>
<td>IKOREL</td>
<td>20 mg</td>
<td>tablet</td>
<td>oral use</td>
</tr>
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<td>France</td>
<td>Sanofi-Aventis France 1-13 boulevard Romain Rolland 75014 Paris France</td>
<td>NICORANDIL ZENTIVA</td>
<td>10 mg</td>
<td>scored tablet</td>
<td>oral use</td>
</tr>
<tr>
<td>Member State (in EEA)</td>
<td>Marketing authorisation holder</td>
<td>Invented Name</td>
<td>Strength</td>
<td>Pharmaceutical form</td>
<td>Route of administration</td>
</tr>
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<tr>
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<td>NICORANDIL ZENTIVA</td>
<td>20 mg</td>
<td>tablet</td>
<td>oral use</td>
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<td>France</td>
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<td>Adancor</td>
<td>10 mg</td>
<td>scored tablet</td>
<td>oral use</td>
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<tr>
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<td>Adancor</td>
<td>20 mg</td>
<td>tablet</td>
<td>oral use</td>
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<td>IKOREL</td>
<td>10 mg</td>
<td>tablet</td>
<td>oral use</td>
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<tr>
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<td>IKOREL</td>
<td>20 mg</td>
<td>tablet</td>
<td>oral use</td>
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<td>10 mg</td>
<td>tablet</td>
<td>oral use</td>
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<tr>
<td>Member State (in EEA)</td>
<td>Marketing authorisation holder</td>
<td>Invented Name</td>
<td>Strength</td>
<td>Pharmaceutical form</td>
<td>Route of administration</td>
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<tr>
<td>Portugal</td>
<td>Merck, S.A. Edifício DUO Miraflores Alameda Fernão Lopes, nº 12 - 4º B, 1495-190 Algés Portugal</td>
<td>Dancor</td>
<td>10 mg</td>
<td>tablet</td>
<td>oral use</td>
</tr>
<tr>
<td>Portugal</td>
<td>Merck, S.A. Edifício DUO Miraflores Alameda Fernão Lopes, nº 12 - 4º B, 1495-190 Algés Portugal</td>
<td>Dancor</td>
<td>20 mg</td>
<td>tablet</td>
<td>oral use</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Aventis Pharma Limited One Onslow Street Guildford Surrey GU1 4YS UK</td>
<td>IKOREL</td>
<td>10 mg</td>
<td>tablet</td>
<td>oral use</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Aventis Pharma Limited One Onslow Street Guildford Surrey GU1 4YS UK</td>
<td>IKOREL</td>
<td>20 mg</td>
<td>tablet</td>
<td>oral use</td>
</tr>
</tbody>
</table>
Annex II

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation
**Scientific conclusions**

**Overall summary of the scientific evaluation of Ikorel and associated names, and Dancor and associated names** (see Annex I)

Nicorandil is a vasodilator agent used to treat angina. 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. Ikorel and Dancor medicinal products are registered and marketed in the following EU Members States: Austria, Denmark, France, Ireland, the Netherlands, Portugal and United Kingdom. They are also available in the EU under other trade names: Adancor, Angicor and Nicorandil Zentiva. Nicorandil was synthesised and developed by Chugai Pharmaceutical Co., Ltd in 1975 as a product producing coronary vasodilatation.

Due to the divergent national decisions taken by Member States (MS) concerning the authorisation of Ikorel and its associated names and Dancor and its associated names, these products were included in the list of products for Summary of Product Characteristics (SmPC) harmonisation, requested by the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh). The European Commission notified the European Medicines Agency/ Committee for Medicinal Products for Human Use (EMA/CHMP) secretariat of an official referral under Article 30 of Directive 2001/83/EC in order to resolve divergences amongst the nationally authorised product information (PI) for the above-mentioned products and thus to harmonise them across the EU.

Pre-referral meetings between the EMA and marketing authorisation holders (MAHs) were held. The CHMP addressed a list of questions to the MAHs, pointing out the sections of the products SmPC where divergences existed. Several sections of the summary of product characteristics were assessed and reworded. Hereafter it is summarised the main points discussed for the harmonisation of the different sections of the SmPC.

**Section 4.1 - Therapeutic indications**

i. **Angina pectoris**

Nicorandil has dual pharmacological effects; activation of ATP-sensitive inward-rectifier potassium channels and (similar to nitroglycerin) increased production of nitric oxide. The net effect is to reduce ventricular preload and afterload.

Efficacy in the clinical programme was based on the measurement of anginal attack rates on exercise tests. The main objective criterion of efficacy was exercise capacity reported in terms of time to onset of angina, total exercise duration and time to 1 mm ST segment depression. In addition to its anti-anginal properties, nicorandil is thought to have cardio protective properties.

Several clinical studies\(^1\),\(^2\),\(^3\),\(^4\) in patients with angina pectoris have shown that treatment with nicorandil 10 and 20 mg twice daily prolongs the time to onset of ischemia during exercise and the total exercise duration.


The anti-ischemic activity of nicorandil seems to be comparable to that of diltiazem, nifedipine, nitrates and propranolol.

The half-life of 6 to 8 hours permits twice daily dosage, and total-daily dosages between 10 and 40 mg have been effective in patients with chronic stable angina.

Overall, nicorandil shows moderate efficacy to improve exercise capacity versus placebo and seems to be comparable to other anti-anginal therapies.

The Current Guidelines from the European Society of Cardiology (ESC) for the management of stable angina pectoris dated on 2013 provide the following recommendations for the use of nicorandil in pharmacological therapy to improve symptoms and/or reduce ischaemia in patients with stable angina:

- In case of beta-blocker intolerance or poor efficacy attempt monotherapy with a calcium channel blocker (CCB): use long-acting nitrate, or nicorandil (Class I, level of evidence C).
- If CCB monotherapy or combination therapy (CCB with beta-blocker) is unsuccessful, substitute the CCB with a long-acting nitrate or nicorandil. Be careful to avoid nitrate tolerance (Class IIb, level of evidence C).

Taking the above into account the CHMP was of the view that for the treatment of symptomatic stable angina, nicorandil should be considered in second line. The proposed indication should be revised as follows:

*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 anti-anginal therapies (such as beta-blockers and/or calcium antagonists).

### ii. Prevention of cardiovascular events in patients with stable coronary heart disease (CHD)

Efficacy of nicorandil on cardiovascular risk in patients with stable angina mainly lays on the pivotal study IONA and the supportive study by Nishimura (2009) which enrolled a too small number of patients to assess efficacy on morbi-mortality endpoints appropriately. Others studies did not enrol patients with stable angina and thus are not relevant to evaluate its efficacy for the treatment of angina.

IONA is the only study showing a beneficial effect of nicorandil associated with standard anti-anginal therapy on the prevention of cardiovascular events in patients with stable angina. However, the primary endpoint is weak as it includes the criterion "reduction of hospitalisation" which is subjective criteria for cardiovascular prevention in patient with coronary heart disease (CHD) patients with angina. Furthermore, the composite of the 3 heterogeneous criteria of this primary endpoint, cardiovascular death, myocardial infarction (MI) and hospitalisation, is mainly

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5 ESC guidelines on the management of stable coronary artery disease European Heart Journal (2013) 34, 2949–3003
driven by reduction of hospitalisation with marginal significance (p=0.014). Furthermore, the secondary endpoint, the composite of cardiovascular death and MI, does not reach statistical significance and thus confirms the weakness and irrelevancy of the primary endpoint. In addition, this study is limited by the enrolled population with low revascularisation.

The IONA study was conducted at a time when the standard of care of managing patient with CHD was different from that of present times in terms of revascularisation, antianginal strategies etc., and does not allow a conclusion regarding the prevention of cardiovascular events for CHD patients with angina.

Available data on cardiovascular prevention may suggest a favourable effect of nicorandil in reducing cardiovascular risk, mainly by a reduction of hospitalisation. However, strong uncertainties regarding this preventive effect do not allow any recommendation and cannot support such an indication. In addition, the adverse events observed in post market experience outweigh the marginal benefit in prevention of cardiovascular events in patients with stable angina. Therefore, the CHMP is of opinion that this indication is not supported due to lack of appropriate data.

While the IONA study does not provide adequate support for a prevention indication, the totality of the data, including IONA, provide good support for the new symptomatic indication proposed above.

The CHMP was therefore of the view that the indication of cardiovascular prevention was not further supported.

Section 4.2 - Posology and Method of Administration

Most studies were performed using 10 mg b.i.d. and then 20 mg b.i.d.. Thus, the endpoints were analysed for the 20 mg b.i.d. posology.

One study performed by Meany and colleagues8 (1989) on 46 patients, compared nicorandil 10 mg b.i.d. and 20 mg b.i.d. to placebo. In that study, nicorandil 10 mg b.i.d. was as effective as 20 mg b.i.d. in increasing time to onset of angina and in reducing time to 1-mm ST depression. Nicorandil 20 mg was more effective in reducing resting systolic blood pressure (SBP) and increasing total exercise work load (55% vs 94%). Considering the low number of patients enrolled in this study, no conclusion regarding the efficacy of 10 mg b.i.d. vs 20 mg b.i.d. was possible to draw.

However, the important identified risk of ulceration (gastrointestinal (GI), skin, mucosal, genital and ocular) and perforations, fistula and abscesses has been recognized and monitored since 1997. It appears that most cases, beside GI ulcerations, were reported at a higher dose than 20 mg/day. There is a strong increase in adverse events such as GI ulceration, skin ulceration, GI haemorrhage occurring at 40 mg per day. The number of patients treated by nicorandil per dosage is unavailable; it is thus unknown whether a dose reduction would allow a reduction in ulceration without lack of efficacy.

To conclude, it appears that the dose of 20 mg b.i.d. increases the risk of ulceration, and does not guarantee a safe use for a symptomatic treatment. Consequently, as none of the performed studies show efficacy at doses lower than 20 mg b.i.d., and as the toxicity is dose dependant and appears at 20 mg b.i.d., the indication should be restricted to second line treatment as recommended in section 4.1 for safety reasons.

This risk of ulcerations was mainly established based on safety reports received in association with the marketed product. Event counts were presented by the different daily doses in the previous Periodic Safety Update Report for nicorandil (reporting period 01-March-2010 to 28-February-2013).

In the context of ulceration, early diagnosis of ulcerations and nicorandil withdrawal appear to be the most adequate measure leading to healing and prompt recovering. With the current knowledge, the early diagnosis and the identification of nicorandil treatment as a possible cause to the emergence of ulceration are the best way to prevent more severe ulceration and to ensure recovery. The information/education to gain a knowledge that allows this diagnosis is the best risk minimisation measure identified so far.

The step of a retrospective assessment as part of the pharmacovigilance plan is a pre-requisite for a thorough understanding of the factors leading to the development of ulcerations.

In addition a PASS, retrospective study based on a patient cohort, is already planned by the MAHs. The objectives are to quantify the rates of ulceration in patients treated with nicorandil (including but not restricted to gastrointestinal, skin, ocular, mucosal, anal sites; alone or in multiple locations), as well as subsequent erosion, perforation, haemorrhage, abscess formation, fistulae and delayed wound healing in a real world setting; together with identification of high risk subgroups, other risk factors, and a dose and time effect assessment.

The results of this PASS are awaited in Q1 2015. In the meantime, it is acknowledged by the CHMP that in the context of ulceration, early diagnosis of ulcerations and nicorandil withdrawal appear to be the most adequate measure leading to healing and prompt recovering.

According to the risk management plan assessed separately in a worksharing procedure9, a DHPC emphasising the risk of ulceration is already planned to be disseminated in all member states. The CHMP considers that the DHPC should also inform about the main modifications of the product information following the outcome of this harmonisation procedure; this should be decided at national level by each competent authority, if deemed necessary. For consistency the MAHs should provide a common DHPC, if required by the national authority. The MAHs should evaluate the impact of this DHPC after it is sent out.

The CHMP noted that the daily dose in Asiatic patients is below the one defined in European patients. The European and Asian development plans have been conducted independently in the two different populations.

As specified in the current ICH guidance on “Ethnic factors in the acceptability of foreign clinical data” dated 1998 evaluation of the pharmacokinetics and pharmacodynamics and their comparability in the three major racial groups most relevant to the ICH regions (Asian, Black, Caucasian) is critical to the registration of medicines in the ICH regions.

Five (5) mg nicorandil b.i.d. failed to show any objective improvement in exercise performance as compared to placebo. The statistically significant superiority of a single 5 mg dose over placebo was not considered as relevant evidence for efficacy after repeated dosing, as it was an acute administration only, and this was not the objective of the study. This is in contrast to the dosing schedule in Japan where 5 mg b.i.d. is the recommended starting dose.

However, the 5 mg dose although active in Japanese patients has shown to induce modest haemodynamic changes. In addition, beside a possible difference in response between Caucasian and Japanese (as regards to weight), most of the studies in view of which the 5 mg b.i.d. dose was

9 Procedure UK/H/xxx/WS147 due for finalisation at the end of May 2015 the earliest.
determined, were open uncontrolled protocols. Furthermore Japanese studies with double blind randomised controlled design have used higher single doses, i.e., 10 or 30 mg nicorandil.

Consequently, 10 and 20 mg b.i.d. doses seemed to give the best compromise between efficacy and clinical acceptability. These doses were therefore used in all the major controlled trials. In general, it can be stated, that the treatment should be conducted with the lowest effective dose. Therefore the 20 mg daily dose could not be generalised. The daily dose in Asiatic patients cannot be extrapolated to the European patients; this is acknowledged by the CHMP.

**Special populations**

*Coronary heart disease (CHD) patients*

No dose recommendation is proposed for prevention of CHD events and the product information was adapted accordingly. The dose recommendation for the prevention of CHD events in patients with stable angina pectoris has been deleted from the SmPC.

*Paediatric Patients*

According to the Guideline on SmPC (dated September 2009), available information on pediatric patients should be summarised using some standard statements in section 4.2. The following phrase was recommended regarding the paediatric populations:

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

**Method of administration**

This section was clarified by indicating that the tablets should not be removed from the blister strip until intake (with cross references to the sections 4.4 and 6.4) as they are affected by humidity and mentioning of the absence of effect with food intake.

**Section 4.3 – Contraindications**

There were no major discrepancies between the existing wordings in the different SmPCs. However, two contraindications related to the risk of acute pulmonary oedema and hypovolemia were added in this section.

**Section 4.4 – Special warnings and precautions for use**

Initially lack of glucose-6-phosphate-dehydrogenase was added as contraindication. However this was based on limited evidence via literature\(^\text{10}\) (Ekanayaka, 2014).

Nicorandil may act partly through the nitrate moiety, which seems to be the trigger of methemoglobinemia through an oxidation process. However, the CHMP is of the view that the level of the oxidation process may not be clinically relevant as only a single case of methemoglobinemia was reported.

has been reported with the use of nicorandil. Therefore, a contra-indication is not considered justified, however a warning statement is requested by the CHMP. This should reflect that nicorandil should be used with caution in patients with glucose-6-phosphate-dehydrogenase deficiency as this may lead to methemoglobinemia based on the theoretical mechanism of triggering this process by metabolism of organic nitrates resulting in the formation of nitrites.

In addition, two hemodynamic studies (SG 002 and EMD 034) studied hemodynamic effects of single oral doses of nicorandil (40 mg, 60 mg, 80 mg) in a total of 21 pharmacodynamically evaluable patients with severe heart failure (N.Y.H.A. class III and IV). The SG 002 study was an open label non-controlled study and EMD 034 study was a double-blind randomized cross over study. The hemodynamic results led to the conclusion that nicorandil produced a beneficial effect in congestive heart failure (CHF) evaluated patients, by exerting an unloading effect and improving cardiac pump function.

The reduction in preload was proportionally more important than that of the afterload. The effect on venous capacitance was less than with nitrates. Postural hypotension was observed, although only after the first administration, whether it was 40 or 60 mg.

However, there is no available data regarding the efficacy of nicorandil repeated oral administration in patients with cardiac failure NYHA III-IV classes.

There is a lack of clinical data concerning the safety of the use of nicorandil in cardiac failure NYHA III-IV. The CHMP therefore requested the MAHs to include a statement mentioning that nicorandil should be used with caution in such a population.

**Section 4.5 - Interaction with other medicinal products and other forms of interaction**

Nicorandil may induce hyperkalaemia. Hyperkalaemia occurs infrequently with NSAIDs. It is more likely to occur in patients with specific risk factors such as those receiving potassium supplements or potassium-sparing diuretics.

Therefore, the simultaneous administration of nicorandil with NSAIDs can increase the risk of hyperkalaemia due to a synergistic effect.

Nicorandil may also induce gastrointestinal ulceration, perforation and haemorrhage; therefore, the simultaneous administration of nicorandil with NSAIDs can increase the risk of gastrointestinal ulceration, perforation and haemorrhage due to a synergistic effect. NSAIDs can cause clinically important damage of the gastrointestinal tract, increasing the incidence of bleeding in the upper gastrointestinal tract and of perforation, although serious complications and death are relatively infrequent. They have also been associated with damage to the distal small intestine and colon.

Therefore a statement regarding the interaction with NSAIDs was recommended by the CHMP for this section of the SmPC, making also a cross reference to section 4.4.

*In patients concomitantly receiving NSAIDs including acetylsalicylic acid for both cardiovascular prevention and anti-inflammatory dosages, 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 CHMP also recommended the information on the absence of pharmacodynamic interaction between nicorandil and acenocoumarol to be reflected in the SmPC with a cross reference to section 4.4 in order to refer the physician to the risk of ulcerations and associated bleeding.

**Section 5.1 - Pharmacodynamic properties**

This section of the SmPC has been harmonised to include the relevant available information.

The mechanism of action of nicorandil as a nicotinamide ester was clarified and the wording harmonised.

Nicorandil 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 (GMP). This results in an increased pooling in capacitance vessels with a decrease in preload.

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 noradrenaline.

Nicorandil has no direct effect on myocardial contractility.

The results of the IONA study were summarised following the same wording for both groups of products. In summary 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 anti-anginal therapies and at high risk of cardiovascular events defined by either previous myocardial infarction, or coronary artery bypass grafting, or coronary artery disease confirmed by angiography, or a positive exercise test in the previous two years. In addition one of the following was also in force: left ventricular hypertrophy on the ECG, left ventricular ejection fraction ≤45%, or an end diastolic dimension of >55mm, age ≥65, diabetes, hypertension, peripheral vascular disease, or cerebrovascular disease.

**Section 5.2 - Pharmacokinetic properties**

This section of the SmPC has been harmonised to clarify and harmonise the relevant available information.

**Section 5.3 – Preclinical safety data**

This section of the SmPC has been harmonised to include the relevant available information. The impairment of fertility and the embryotoxicity and peri- and post-natal toxicity were clarified.
Labelling

The labelling was reviewed during this procedure. No changes were introduced.

Package Leaflet

Following all the changes in the SmPC there were amendments made to the package leaflet (PL). The final PL wording was agreed by the CHMP.
**Grounds for the variation to the terms of the marketing authorisations**

In conclusion, based on the assessment of the MAHs’ proposals and responses and following the discussions of the Committee, the CHMP adopted harmonised sets of product information documents of Ikorel and associate names and Dancor and associated names.

Whereas

- the scope of the referral was the harmonisation of the summary of products characteristics, labelling and package leaflet;
- the summary of products characteristic, labelling and package leaflet proposed by the Marketing Authorisation Holders have been assessed based on the documentation submitted and the scientific discussion within the Committee;

the CHMP was of the opinion that the benefit/risk ratio of Ikorel and associated names and Dancor and associated names is considered to be favourable. The CHMP adopted a positive opinion recommending the variation to the terms of the marketing authorisations for which the summary of products characteristics, labelling and package leaflet as set out in Annex III of the CHMP opinion for Ikorel and associated names and Dancor and associated names (see Annex I).
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.
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 QUANTITATIVE 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.

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Dizziness</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Eye disorders</td>
<td></td>
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<td></td>
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<tr>
<td>Cardiac disorders</td>
<td>Heart rate increased</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Adverse Reaction Category</td>
<td>Very common</td>
<td>Common</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Very rare</td>
<td>Not known</td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
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<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td>Cutaneous</td>
<td>Decrease in blood pressure</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>vasodilatation</td>
<td>(see section 4.4)</td>
<td></td>
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<td></td>
<td></td>
<td>with flushing</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td>Vomiting,</td>
<td>Gastrointestinal ulcerations</td>
<td>Gastrointestinal haemorrhage</td>
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<tr>
<td></td>
<td></td>
<td>nausea</td>
<td>(stomatitis, aplhtosis, mouth ulcer, tongue ulcer, small intestinal ulcer, large intestinal ulcer, anal ulcer) (see below and section 4.4)</td>
<td>(see section 4.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
<td></td>
<td>Liver disorders such as hepatitis, cholestasis, or jaundice</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td>Rash, pruritus</td>
<td>Angioedema, Skin and mucosal ulcerations (mainly peri-anal ulcerations, genital ulcerations and parastomal ulcerations) (see section 4.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td>Myalgia</td>
<td></td>
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<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td>Feeling of</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>weakness</td>
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</tbody>
</table>

**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).
### 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 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

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.
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}