

## **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 re worded. 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<sup>1,2,3,4</sup> 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.

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<sup>1</sup> Hughes LO, Rose EL, Lahiri A, et al. Comparison of nicorandil and atenolol in stable angina pectoris. Am J Cardiol. 1990; 66(7):679-82.

<sup>2</sup> Meeter K, Kelder JC, Tijssen JG, et al. Efficacy of nicorandil versus propranolol in mild stable angina pectoris of effort: a long-term, double-blind, randomized study. J Cardiovasc Pharmacol 1992;20(Suppl 3):S59-66.

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<sup>5</sup> 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<sup>6</sup> and the supportive study by Nishimura<sup>7</sup> (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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<sup>3</sup> Guermonprez JL, Blin P, Peterlongo F. A double-blind comparison of the long-term efficacy of a potassium channel opener and a calcium antagonist in stable angina pectoris. Eur Heart J. 1993; 14 Suppl B: 30-4.

<sup>4</sup> Ulvenstam G, Diderholm E, Frithz G, et al. Antianginal and anti-ischemic efficacy of nicorandil compared with nifedipine in patients with angina pectoris and coronary heart disease: a double-blind, randomized, multicenter study. J Cardiovasc Pharmacol 1992; 20(Suppl 3):S67-73.

<sup>5</sup> ESC guidelines on the management of stable coronary artery disease European Heart Journal (2013) 34, 2949–3003

<sup>6</sup> The IONA Study group: Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in angina (IONA) randomized trial. Lancet 2002; 359: 1269-1275

<sup>7</sup> Nishimura M, Tokoro T, Nishida M, et al. Oral nicorandil to reduce cardiac death after coronary revascularization in hemodialysis patients: a randomized trial. Am J Kidney Dis. 2009 Aug; 54(2): 307-17

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 colleagues<sup>8</sup> (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.

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<sup>8</sup> Meany TB, Richardson P, Camm AJ, et al. Exercise capacity after single and twice-daily doses of nicorandil in chronic stable angina pectoris. *Am J Cardiol.* 1989;63(21):66J-70J.

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 procedure<sup>9</sup>, 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

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<sup>9</sup> 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<sup>10</sup> (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

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<sup>10</sup> Ekanayaka RA. A case of pseudocyanosis. Case Rep. BMJ, 2014, Mar 10.

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 noradrenalin.

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  $\leq 45\%$ , or an end diastolic dimension of  $>55\text{mm}$ , age  $\geq 65$ , 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).