Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nicozone 20 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Nicorandil 20 mg tablet contains 20 mg nicorandil.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
White to off-white round, flat tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

The prevention and long term treatment of chronic stable angina pectoris.

4.2 Posology and method of administration

For oral use.

Adults
The recommended starting dose is 10 mg nicorandil twice daily, preferably in the morning and in the evening.

A lower starting dose of 5 mg twice daily may be employed (for a few days) in patients particularly susceptible to headache.

Subsequently the dosage should be titrated upwards depending on the patient's clinical response and tolerance.

The usual therapeutic dosage is in the range of 10 to 20 mg nicorandil twice daily, although up to 30 mg twice daily may be employed, if necessary.

Elderly
For elderly patients use of the lowest effective dose is recommended.

Paediatric Population
Nicozone 20 mg tablets are not recommended for use in children and adolescents below 18 years due to insufficient data on safety and efficacy.

4.3 Contraindications

Nicozone 20 mg tablets are contraindicated in patients with hypersensitivity to nicorandil or to any of the excipients.

Nicorandil must not be used in the case of cardiogenic shock, hypotension, or left ventricular failure with low filling pressure.

Concurrent use of nicorandil and phosphodiesterase 5 inhibitors is contraindicated, since it can lead to a serious drop in blood pressure.

4.4 Special warnings and precautions for use

Gastrointestinal ulcerations, skin and mucosal ulcerations have been reported with nicorandil. These are refractory to treatment and most only respond to withdrawal of nicorandil treatment. If ulcerations develop, it is recommended to discontinue the nicorandil treatment.

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

Nicorandil must be used with caution patients who may have blood volume depletion or in those who present, low systolic blood pressure (e.g. below 100 mm Hg), acute pulmonary oedema or acute myocardial infarction with acute left ventricular failure and low filling pressures.

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

The tablets are sensitive to moisture; hence the patients should be advised to keep the tablets in their blister until intake.

Paediatric patients
Nicozone 20 mg is not recommended in paediatric patients since its safety and efficacy have not been established in this patient group.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent use of nicorandil and phosphodiesterase 5 inhibitors, e.g. sildenafil, tadalfil, vardenafil, is contraindicated, since it can lead to a serious drop in blood pressure.

Therapeutic doses of nicorandil may lower the blood pressure of hypotensive patients. If nicorandil is used concomitantly with antihypertensive agents or other medicinal products with blood-pressure-lowering effect (e.g. vasodilators, tricyclic antidepressants, alcohol) the blood-pressure-lowering effect may be increased.

4.6 Fertility, pregnancy and lactation

Pregnancy
Although animal studies have not shown any teratogenic effect of nicorandil, the medicinal product has not been studied in human pregnancy; therefore, Nicozone 20 mg must only be used in pregnant women if the anticipated benefit outweighs any potential risks.

Lactation
Animal studies have shown that nicorandil is excreted in small amounts into the breast milk. It is not known whether nicorandil is excreted in human milk, therefore Nicozone 20 mg is not recommended during breastfeeding.

Fertility
Nicorandil was not shown to alter fertility in animal studies. There are no human data.

4.7 Effects on ability to drive and use machines

Blood pressure-lowering effects of nicorandil can reduce the ability to drive or to use machines. This effect can be increased in conjunction with alcohol or other products with blood-pressure-lowering effect (e.g. vasodilators, tricyclic

antidepressants). (see section 4.5).

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

4.8 Undesirable effects

The following definitions apply to the frequency terminology used hereafter:

Very common (≥ 1/10), Common (≥ 1/100, < 1/10), Uncommon (≥ 1/1,000, < 1/100)
Rare (≥ 1/10,000, < 1/1,000), Very rare (< 1/10,000)

Frequency **System organ class**	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**
Nervous system disorder	Headache, particularly during the first few days of treatment.	Dizziness			
Cardiac disorders		Increase in heart rate, following the administration of high doses.	Tachycardia (at high doses)	Palpitation	
Vascular disorders		Cutaneous vasodilation with flushing	Decrease in blood pressure		
Gastrointestinal disorders		Nausea, vomiting		Gastrointestinal ulcerations such as aphthosis, mouth ulcers, tongue ulcers, intestinal and anal ulcers. These ulcers, if advanced, may develop into perforation, fistula, or abscess formation. (see section 4.4).	
Hepatobiliary disorders					Liver disorders such as hepatitis cholestasis, or jaundice.
Skin and				Different types	Angio-

subcutaneous tissue disorders				of rash, pruritis	oedema, 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		Feeing of weakness			

Additional Information
In addition, the following events have been reported at a different frequency in the IONA (Impact of Nicorandil in Angina) study which was conducted in subjects at high risk of cardiovascular events only.

Skin and subcutaneous tissue disorders
Uncommon: Angioedema

Gastrointestinal disorders
Common: Rectal bleeding.
Uncommon: Mouth ulcers
Very Rare: Abdominal pain.

Musculoskeletal and connective tissue disorders
Uncommon: Myalgia

4.9 Overdose

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

Management
Monitoring 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.

There is no experience of massive overdose in humans. The LD50 of nicorandil in rodents following oral administration is of the order of 1200 mg/kg, and of 62.5-125 mg/kg in dogs.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

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

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

5.2 Pharmacokinetic properties

Nicorandil is well absorbed with no significant first-pass metabolism. Maximum plasma concentrations are achieved in 30 to 60 minutes and are directly related to the dosage. Metabolism is mainly by denitration of the molecule into the nicotinamide pathway with less than 20% of an administered dose being excreted in the urine. The main phase of elimination has a half-life of about 1 hour. Nicorandil is only slightly bound to plasma proteins.
No clinically relevant modifications in the pharmacokinetic profile have been seen in the elderly or in patients with liver disease or chronic renal failure.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, acute- and repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.
Effects observed in reproductive toxicity studies (increased pre-implantation loss, fetal mortality and peri-natal mortality) and in repeated dose toxicity studies (testicular and skeletal muscle damage in rats and cardiovascular effects in dogs) were seen at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium starch glycolate (Type A)
Mannitol
Stearic Acid

6.2 Incompatibilities

Not applicable

6.3 Shelf life

15 months.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

The tablets are supplied in polyamide /Aluminium/PE/desiccant/PE-Alu/PE blisters of 10 tablets.

Pack size: 20, 30 and 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Helm AG
Nordkanalstrasse 28
20097 Hamburg
Germany

8 MARKETING AUTHORISATION NUMBER

PA 1466/2/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9th September 2011

10 DATE OF REVISION OF THE TEXT