Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ikorel tablets 10 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Nicorandil 10 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Product imported from the UK:
Round, off-white, circular tablets with faceted edges, scored on one side and with the marking 'IKI0' on the other side.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ikorel is indicated for the prevention and management of angina pectoris.

4.2 Posology and method of administration

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

Elderly: There are no special dosage requirements for elderly patients, but as with all medicines the lowest effective dose should be used.

Children: Not recommended.

4.3 Contraindications

Nicorandil is contra-indicated in patients with:
- Known idiosyncratic hypersensitivity to nicorandil or any of the excipients
- cardiogenic shock
- severe hypotension
- left ventricular failure with low filling pressures
- acute pulmonary oedema
- myocardial infarction

Due to the severe risk of hypotension, the concomitant use of nicorandil and phosphodiesterase 5 inhibitors (e.g. sildenafil, tadalfil, vardenafil) is contra indicated, since it can lead to a serious drop in blood pressure.

4.4 Special warnings and precautions for use

The use of nicorandil should be avoided in patients with depleted blood volume, low systolic blood pressure (e.g. below 100 mm Hg), acute pulmonary oedema or acute myocardial infarction with acute left ventricular failure and low filling pressure.

Therapeutic doses of nicorandil may lower the blood pressure of hypertensive patients and therefore nicorandil, as with other antianginal agents, should be used with care when prescribed with antihypertensive drugs.

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

Gastrointestinal ulcerations skin and mucosal ulcerations have been reported with nicorandil (see Section 4.8 Undesirable Effects). These are refractory to treatment and most only respond to withdrawal of nicorandil treatment. If ulcerations develop nicorandil should be discontinued.

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

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 patients

Ikorel 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

No pharmacological and/or pharmacokinetic interaction has been observed in animal and human studies with nicorandil associated with beta-blockers, a calcium antagonist, digoxin, a combination of digoxin/frusemide, nicoumalone, rifampicin and cimetidine. The drug may, nevertheless, potentiate the vasodilation associated with alcohol, nitrates, tricyclic antidepressants and antihypertensive drugs administered concurrently.

As hypotensive effects of nitrates or nitric oxide donors are potentialised by phosphodiesterase 5 inhibitors, the concurrent administration of nicorandil and phosphodiesterase 5 inhibitors are contraindicated, (see Section 4.3), since it can lead to a serious drop in blood pressure.

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

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

Although animal studies have not demonstrated a teratogenic effect nor interference with reproduction, there is no experience of use during human pregnancy. The product should not be used during pregnancy unless it is considered essential by the physician.

Small therapeutic insignificant amounts are excreted in breast milk. Use is not recommended during breast feeding.

4.7 Effects on ability to drive and use machines

The product may cause drowsiness or dizziness. The patient should not drive or operate machinery until it has been shown that the drug does not impair physical or mental performance. 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).

4.8 Undesirable effects

The following frequency rating is used, when applicable: Very common ≥ 10%; Common ≥ 1 and < 10%; Uncommon ≥ 0.1 and < 1%; Rare ≥ 0.01 and < 0.1%; Very rare < 0.01%.

Cardiac Disorders:
Common: Increase in heart rate, following the administration of high dose.

Nervous System Disorders:
Very Common: Headache usually of a transitory nature, especially when treatment is initiated.
Common: Dizziness

Gastrointestinal Disorders:
Common: Nausea and Vomiting
Rare: severe cases of painful aphtosis or mouth ulcers
Rare: Gastrointestinal ulcerations, such as stomatitis, mouth ulcer, tongue ulcer, aphthosis, small intestine ulcer, large intestine ulcer and anal ulcer. These ulcers, if advanced, may develop onto perforation, fistulating disease, or abscess formation, (see Section 4.4, Special Warnings and Precautions for use).

Skin and Subcutaneous Tissue Disorders
Rare: different types of rash, pruritus
Very Rare: Angioedema
Unknown: Skin ulcerations (mainly peri-anal ulcerations, genital ulcerations and parastomal ulcerations) (see section 4.4, Special Warnings and Precautions for use).

Musculoskeletal and Connective Tissue Disorders:
Rare: Myalgia

Vascular Disorders:
Common: Cutaneous vasodilation with Flushing
Uncommon: Decrease in blood pressure. Hypotension may occur at high therapeutic doses

General Disorders:
Common: Feeling of Weakness

Hepatobiliary Disorders:
Very Rare: Liver disorders such as hepatitis, cholestasis, or jaundice.

Eye disorders:
Frequency Unknown: Conjunctivitis, conjunctival ulcer and corneal ulcer

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: Angio-edema

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

Musculoskeletal and connective tissue disorders
Uncommon: Myalgia

4.9 Overdose

In case of acute overdose, the likely symptomatology may be peripheral vasodilation with a fall in blood pressure and reflex tachycardia. In such event, monitoring of cardiac function and general supportive measures should be used. If not successful, circulating plasma volume should be increased by fluid resuscitation. In life-threatening situations, administration of vasopressors should be considered. The LD_{50} of nicorandil in rodents following oral administration is of the order of 1200mg/kg, and of 62.5-125mg/kg in dogs.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC CODE: C01DX16

The coronary vasodilating activity of nicorandil is considered to be the consequence of the increasing cyclic GMP production by stimulating guanylyl cyclase in the coronary vascular smooth muscle, similar to other nitrates/nitrites (*in vitro*). In addition, other mechanisms such as hyperpolarization of the cell membrane were investigated concerning its coronary blood flow-increasing and coronary vasospasmolytic effects.

The vasorelaxant effect of nicorandil in isolated blood vessels is suppressed by an ATPsensitive K channel blocker or a guanylate cyclase inhibitor. Moreover, in a canine model of acute heart failure, the cardiac hemodynamics-improving effect of the drug (e.g. effect of increasing the aortic blood flow) was suppressed by an ATP-sensitive K channel blocker. Furthermore, the drug caused an increase in the cGMP content in isolated blood vessels. These facts suggest that the vasodilating effect of the drug is related to the effect of opening the ATP-sensitive K channel, as well as to the effect of increasing production of cGMP.

Clinical / Efficacy Studies
1. Clinical usefulness of nicorandil was indicated through a double-blind controlled clinical trial in comparison with nifedipine in 103 patients and another one in comparison with propranolol in 80 patients with various types of angina pectoris.

2. The IONA Study Group showed a significant improvement in outcome due to a reduction in major coronary events by antianginal therapy with nicorandil in patients with stable angina. 5126 patients were randomly assigned nicorandil (10 mg twice daily for 2 weeks and 20 mg twice daily thereafter) (n=2565) or identical placebo (n=2561) in addition to standard antianginal therapy. There were 398 (15.5%) primary endpoint events in the placebo group and 337 (13.1%) in the nicorandil group (hazard ratio 0.83, 95% CI 0.72 – 0.97; p=0.014).

5.2 Pharmacokinetic properties

Absorption
The pharmacokinetic parameters of nicorandil were observed in 6 healthy adult volunteers after a single oral dose of 10 mg of nicorandil. The plasma concentration was 112.6 + 35.5 (mean + S.E.) ng/mL, 133.5 + 26.3 ng/mL, 104.9 + 14.3 ng/mL, 63.2 + 12.0 ng/mL, 9.9 + 2.5 ng/mL, at 0.25 hours, 0.5 hours, 1.0 hours, 2.0 hours, and 4.0 hours after administration, respectively. The area under the curve (AUC) in steady state was 262.5 + 43.1 hr.ng/mL. The maximum concentration (Cmax) was 152.3 + 29.2 ng/mL at 0.55 + 0.12 hours (Tmax).

Distribution
According to an *in vitro* study using human serum, the serum protein binding rate of the compound was 34.2 to 41.5% (as tested at nicorandil concentrations of 1 to 100 μg/mL)

Metabolism
A metabolism/excretion study performed in 4 healthy adult volunteers administered a single oral dose of 20 mg of [D]-nicorandil revealed that the compound was mostly metabolized via denitration to N-(2-hydroxyethyl) nicotinamide.

The metabolite was found in the plasma as early as 0.5 hour after the administration, reached a peak plasma concentration at 2 hours, and was almost completely eliminated from the plasma by 8 hours. The cumulative urinary excretion rate in 24 hours after dosing was 0.7 to 1.2% of the dose given as nicorandil and 6.8 to 17.3% as its metabolite N-(2-hydroxyethyl) nicotinamide.

Pharmacokinetics in Special Populations
Hepatic Impairment
No formal study of the effect of hepatic impairment on the pharmacokinetics of nicorandil was conducted.
Renal Impairment
Six patients on hemodialysis and 3 patients treated with conservative therapy were compared with 9 controls on pharmacokinetic parameters with nicorandil. Longer halflife period was observed with patients on hemodialysis.

5.3 Preclinical safety data

Carcinogenicity
Carcinogenicity studies found no indication of carcinogenic activity in rats administered with nicorandil for 2 years.

Mutagenicity
Mutagenicity and genotoxicity studies, with and without metabolic activation where appropriate, have shown that nicorandil has no mutagenic activity *in vitro* in either bacterial (Ames test) or mammalian cells (Chinese hamster lung DON)
Nicorandil does not induce chromosomal damage *in vivo* in the mouse micronucleus Assay.

Impairment of Fertility
Fertility studies showed no effects on mating ability in either male or female rats, but decreases of alive fetuses and implantation sites were noted at 50 mg/kg/day and over. Additional investigating studies for testicular toxicity revealed histopathological changes in spermatogenic cells, as well as decreases of blood flow in the testis and testosterone level in the blood. These results suggest that testicular toxicity by nicorandil is related to sustained decrease of blood flow caused by reduction of cardiac output. Upon cessation of treatment, recovery from nicorandil-induced testicular toxicity was observed after 4 weeks, that indicates reversible changes.

Teratogenicity
Teratogenic studies in rats and rabbits indicate that, following exposure to nicorandil at doses that were maternally toxic, there was embryotoxicity observed. There was no evidence of teratogenicity (rats and rabbits), or abnormal pre or postnatal physical or behavioral development (rats). Embryotoxic/teratogenic effects were not observed in rats at 25 mg/kg/day or rabbits at 12.5 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Corn starch
Croscarmellose sodium
Stearic acid
Mannitol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

Each blister strip should be used within 30 days of opening.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Blister strips of 10 tablets per silica gel dessicant. Each tablet is connected via a channel to the dessicant capsule.
Pack size: 60 Tablets

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1562/033/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5th November 2010

10 DATE OF REVISION OF THE TEXT

May 2014