IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PPA1328/025/001
Case No: 2078143

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

B & S Healthcare

Unit 4, Bradfield Road, **Ruislip**, **Middlesex**, **HA4 0NU**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Ikorel 10 mg Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **23/02/2010** until **17/08/2011**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ikorel 10 mg Tablets

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 France and the United Kingdom:
Off-white, circular tablets with faceted edges, scored on one side and with the marking 'IK10' on the other side.

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. 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 hypersensitivity to nicorandil or any of the excipients
- cardiogenic shock
- hypotension
- left ventricular failure with low filing 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.

4.4 Special warnings and precautions for use

Pharmacodynamic Interactions:

Other NSAIDs, including salicylates (acetylsalicylic acid ≥ 3 g/d):
Administration of several NSAIDs together may increase the risk of gastrointestinal ulcers and bleeding, via a synergistic effect. The concomitant use of meloxicam with other NSAIDs is not recommended (see section 4.4).

Diuretics:
Treatment with NSAIDs is associated with potential for acute renal failure, notably in dehydrated patients. Patients receiving meloxicam and diuretics should be adequately hydrated and be monitored for renal function prior to initiating treatment (see section 4.4).

Oral anticoagulants:
Increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa. The concomitant use of NSAIDs and oral anticoagulants is not recommended (see section 4.4).
Careful monitoring of the INR is required if it proves impossible to avoid such combination.

Thrombolytics and antiplatelet drugs:
Increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa.
ACE inhibitors and angiotensin II receptor antagonists:
NSAIDs (including acetylsalicylic acid at doses ≥ 3g/d) and angiotensin-II receptor antagonists exert a synergistic effect on the decrease of glomerular filtration, which may be exacerbated when renal function is altered. When given to the elderly and/or dehydrated patients, this combination can lead to acute renal failure by acting directly on glomerular filtration. Monitoring of renal function at the beginning of the treatment is recommended as well as regular hydration of the patient. Additionally, concomitant treatment can reduce antihypertensive effect of ACE inhibitors and angiotensin II receptor antagonists, leading to partial loss of efficacy (due to inhibition of prostaglandins with vasodilatory effect).

Other antihypertensive drugs (e.g. Beta-blockers):
As for the latter, a decrease of the antihypertensive effect of beta-blockers (due to inhibition of prostaglandins with vasodilatory effect) can occur.

Cyclosporin:
Nephrotoxicity of cyclosporin may be enhanced by NSAIDs via renal prostaglandin mediated effects. During combined treatment renal function is to be measured. A careful monitoring of the renal function is recommended, especially in the elderly.

Intrauterine devices:
NSAIDs have been reported to decrease the efficacy of intrauterine devices.
A decrease of the efficacy of intrauterine devices by NSAIDs has been previously reported but needs further confirmation.

The use of nicorandil should be avoided in patients with depleted blood volume, low systolic blood pressure, 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.
Treatment with nicorandil should be discontinued if persistent aphtosis or mouth ulcer occur.

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 concomitant administration of nicorandil and phosphodiesterase 5 inhibitors are contraindicated, (see Section 4.3).

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

4.6 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.

4.8 Undesirable effects

The following CIOMS 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:
Uncommon: Tachycardia at high dosage

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
Very Rare: Gastrointestinal ulcerations, such as 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).

Skin and Subcutaneous Tissue Disorders
Rare: different types of rash
Very Rare: Angioedema

Musculoskeletal and Connective Tissue Disorders:
Rare: Myalgia

Vascular Disorders:
Common: Flushing
Uncommon: Hypotension may occur at high therapeutic doses

General Disorders:
Common: Feeling of Weakness

Hepatobiliary Disorders:
Rare: Hepatic Function abnormalities

The following additional adverse reactions have been reported during Postmarketing experience; they are derived from spontaneous reports and therefore, the frequency of these adverse reactions is not known:

Skin and Subcutaneous Tissue Disorders
Skin ulcerations (mainly peri-anal ulcerations, gential ulcerations and para-stomal unlcerations).

Eye Disorders;
Diplopia

4.9 Overdose

In case of overdosage, 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 substitution of fluid. 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.
In case of overdosage, 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 substitution of fluid. 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

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 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.

5.2 Pharmacokinetic properties

After oral administration, nicorandil is absorbed rapidly and completely from the gastrointestinal tract. The absolute bioavailability is about 75%. There is no significant hepatic first-pass effect.
Maximum plasma concentrations are reached after about 30 minutes. The plasma concentration (and the area under the curve) show a linear proportionality to the dose. The drug disposition processes (distribution volume, mean residence time, total body clearance and apparent elimination half-life) remain stable whatever the dose in the therapeutic range.
Nicorandil is only slightly bound to human plasma proteins (free fraction estimated at about 75%).
The decrease in plasma concentration reveals two different processes:
A rapid elimination phase with a half-life of about 1 hour, which covers about 96% of the plasma concentration;
A slow elimination phase occurring between the 8th and the 24th hour following the oral dose.

Metabolism takes place mainly via denitration of the molecule with the denitrated product then merging into the nicotinamide pathway. Nicorandil and metabolites are mainly excreted by the kidney. About 21% of the administered dose is eliminated through the urine with about 1% as the unchanged compound and the remaining mainly as the denitrated metabolite (about 7%) and derivatives following denitration (eg nicotinuric acid, nicotinamide, N-methylnicotinamide and nicotinic acid).
Steady state is rapidly achieved during repeated oral administration (bid regimen).
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. Moreover, the metabolism of nicorandil appears not to be significantly modified by cimetidine or rifampicin, respectively an inhibitor and an inducer of liver microsomal mixed-function oxidases.

5.3 Preclinical safety data

After single intravenous, intraperitoneal, subcutaneous and oral administration to rats and mice, intravenous and oral administration to dogs, nicorandil showed that its acute toxicity is low. Oral LD_{50} values varied between 1100 and 1310mg/kg in rodents and 62.5 and 125mg/kg in dogs.
Upon repeated oral administration to dogs and rats for periods up to 12 months and at doses ranging between 5mg/kg (equivalent to about 3 times the human dose in terms of plasma level) and 400mg/kg (well exceeding 700 times the human dose in terms of plasma level), nicorandil has been shown to produce, more in the dog than in the rat, transitory symptoms linked to its vasodilating properties, such as reddening of the skin and mucosae, jugular pulse, tachycardia and increased water consumption. In addition to these transitory symptoms, at high dose levels nicorandil also produced some other effects. Testicular and muscular (skeletal) damage was seen in rats and cardiovascular changes were seen in dogs. The testicular damage in rats treated with 200mg/kg can be attributed to the reduced testicular blood flow, measured already at single doses of 10mg/kg. The muscular damage in rats was only observed at 400mg/kg. The cardiovascular effects seen in dogs, such as subendocardial necrosis, haemorrhages in the right atrium, as well as the testicular and muscular damage are considered to be related to exaggerated pharmacological effects of hypotensive agents.
Foetotoxicity, peri- and post-natal toxicity, fertility, mutagenicity and carcinogenicity studies did not reveal any adverse effect of nicorandil under the experimental conditions.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Croscarmellose sodium
Stearic acid
Mannitol (E421)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product shall be 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 25^0C. Store in the original package.

6.5 Nature and contents of container

Blister strips of 10 tablets per silica gel desiccant. Each tablet is connected via a channel to the desiccant capsule.
Pack size: blister pack of 30 or 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

B&S Healthcare
Unit 4
Bradfield Road
Ruislip
Middlesex
HA4 0NU
United Kingdom

8 Parallel Product Authorisation Number

PPA 1328/25/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 18th August 2006

10 DATE OF REVISION OF THE TEXT

February 2010