IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0711/016/001
Case No: 2023417

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

Rowex Ltd

Bantry, **Co. Cork**, **Ireland**

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

Verap 40 Milligram 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 **05/10/2006**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Verap 40mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains verapamil hydrochloride 40.00 mg.

Excipient: Each tablet contains lactose monohydrate 22.0 mg

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, round, biconvex, film-coated tablet with a score notch. The score notch is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

VERAP Tablets are indicated for the treatment of angina pectoris including Prinzmetal angina, supraventricular tachycardia and mild to moderate essential hypertension.

4.2 Posology and method of administration

Route of Administration: Oral.

Recommended Dosage Schedule

Adults only

Verapamil should not be taken with grapefruit juice (see Interactions 4.5)

VERAP Tablets:

Angina including Prinzmetal Angina:
The usual dose is 120 mg three to four times daily. A dose of 80 mg t.i.d. may be adequate in many patients with angina of effort, doses below 120 mg t.i.d. are unlikely to be effective in angina of rest and Prinzmetal's angina.

Supraventricular Tachycardia:
The usual dose is 40 mg to 120 mg three to four times daily according to the severity of the condition.

Essential Hypertension:
The usual dose is 40 mg to 120 mg three to four times daily. In long term treatment a total daily dose of 480 mg should not be exceeded.

4.3 Contraindications

VERAP is contra-indicated in-patients who are hypersensitive to Verapamil Hydrochloride, the active ingredient of the tablets.

VERAP should not be administered in the following cases:

- cardiovascular shock
- recent cardiac infarction with complications [bradycardia, pronounced hypotension, left ventricular insufficiency].
- grade II and grade III atrioventricular block
- sinu-atrial blockage
- sick sinus syndrome [bradycardia – tachycardia syndrome].

4.4 Special warnings and precautions for use

When treating hypertension with VERAP monitoring of the patients blood pressure at regular intervals is required. Particularly careful monitoring is necessary in the following cases:

- 1st degree atrioventricular block
- hypotension [systolic blood pressure below 90 mm Hg]
- bradycardia [pulse below 50 bpm]
- atrial fibrillation/flutter
- simultaneous pre-excitation syndrome

The effect of VERAP is intensified and prolonged in patients with impaired hepatic function due to diminished drug metabolism. In these patients dosage intervals should be prolonged and low doses used.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Verapamil should not be taken with grapefruit juice because its metabolism may be inhibited.

The following drug interactions occur with the simultaneous administration of VERAP.

Anti-arrhythmic drugs, Beta adrenergic blocking agents [Beta-blockers], Inhalation anaesthetics
Synergistic increase in the cardiovascular effects [more severe atrioventricular block, more significant decrease in the cardiac frequency, occurrence of cardiac insufficiency, dramatic drop in blood pressure].

Antihypertensive drugs
Stronger antihypertensive effect.

Digoxin
Increase in the plasma digoxin concentration due to diminished renal excretion. [As a precaution, heed symptoms of a digoxin overdose and, if necessary, reduce glycoside dose, possibly after determining the plasma digoxin concentration].

Quinidine
A greater drop in blood pressure and pulmonary oedema are possible.

Carbamazepine
Carbamazepine effect is increased.

Cimetidine, Ranitidine
Increase in the plasma verapamil concentration is possible.

Lithium
Weakened effect of lithium, increased neurotoxicity.

Rifampicin, Phenytoin, Phenobarbital
Decreased plasma concentration and weakened effect of verapamil.

Theophylline, Prazosin, Cyclosporin
Increased plasma concentration of theophylline, prazosin and cyclosporin, respectively.

Muscle Relaxants
Possible increase in efficacy with verapamil.

Beta-receptor blockers should not be administered intravenously during the treatment with verapamil [exception: intensive care medicine].

4.6 Pregnancy and lactation

VERAP should not be given during pregnancy [especially in the first trimester] and lactation, unless in the doctors judgement, it is essential for the patients well being.

4.7 Effects on ability to drive and use machines

As patients may experience individually different reactions to the drug, the ability to drive in traffic or to operate machines can be impaired. This applies especially at the beginning of treatment and when changing preparations as well as when taken together with alcohol.

4.8 Undesirable effects

The intake of verapamil – especially at higher doses and/or with corresponding previous cardiac impairment – can be associated with side effects pertaining to cardiac conduction [atrioventricular block], cardiac frequency [sinus bradycardia], blood pressure [drop in blood pressure] and cardiac output [cardiac insufficiency].

Constipation is frequently reported.

Dizziness, giddiness, nervousness, headaches, fatigue, paresthesia such as tingling sensation and numbness, nausea, heartburn, malleolar oedema and flush may occasionally occur.

Allergic reactions such as skin rash [exanthema], itching [urticaria], painful reddening of the skin [erythromelalgia] and spasmodic condition of the bronchial musculature [bronchospasms] are rare.

Myalgia or arthralgia are very rare.

Some isolated cases of angioneurotic oedema and Stevens-Johnson syndrome have been observed.

Isolated cases of reversible increase in the serum transaminases and/or alkaline phosphatase have been observed – with such probably due to allergic hepatitis.

Very rare cases of gynaecomastia have been observed in older patients receiving long-term therapy; however the condition subsided in all cases after withdrawing the medication. Increases in the prolactin level have been reported.

The occurrence of changes in the gums [gingival hyperplasia] with longer-term treatment is extremely rare, with such completely disappearing after drug withdrawal.

High blood pressure treatment with verapamil requires regular medical supervision.

4.9 Overdose

The following are the predominant symptoms of overdosage – drop in blood pressure, shock symptoms, unconsciousness, life-threatening dysrhythmias in the form of bradycardia and tachycardia [e.g. sinus arrest, grade III atrioventricular block, escape rhythms, asystolia].

The treatment of overdosage depends upon the type and severity of symptoms. A thorough gastric lavage, possibly also in combination with lavage of the small intestine is indicated after oral intake.

The specific antidote is calcium, e.g. 10 – 20 ml calcium gluconate solution i.v. [2.25 – 4.5 mmol] if necessary by repeated injection or continuous infusion [e.g. 5 mmol/hr].

The usual emergency measures for acute cardiovascular collapse should be applied and followed by intensive care. In cases of second and third degree AV block, atropine, isoprenaline, orciprenaline and if required pacemaker therapy should be considered. If there are signs of myocardial insufficiency dopamine, dobutamine, cardiac glycosides or calcium gluconate [10 – 20 ml of a 10% solution] should be administered.

In the case of hypotension after appropriately positioning the patient dopamine, dobutamine, noradrenaline may be given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: C08DA01
Pharmacotherapeutic group: Phenylalkylamine derivatives
Verapamil belongs to the substance group known as calcium antagonists. These substances have an inhibitory effect on the calcium influx via muscle cell membranes. Verapamil also acts as a calcium antagonist on smooth muscles, affecting particularly the vessels and the gastrointestinal tract. The effect on the smooth vascular muscles is expressed as vasodilatation. As a calcium antagonist, verapamil exerts a distinct effect on the myocardium.

The effect on the atrioventricular node is seen in the form as a prolongation of the conduction time. A negative-inotropic effect can be exerted on the active myocardium.

In humans, verapamil causes a decrease in the total peripheral resistance due to the vasodilation; however, a reflectory increase in the cardiac output does not occur. The result is a corresponding drop in the blood pressure.

5.2 Pharmacokinetic properties

After oral administration, 80-90% of the verapamil is rapidly absorbed from the small intestine. The systemic availability of the unchanged active substance is only approximately 20% due to a marked first-pass effect. A significantly higher systemic availability after oral administration of verapamil must be expected in patients with cirrhosis of the liver. The maximum plasma concentration [C max] of verapamil is achieved 1-2 hours after oral administration.

The proportion of verapamil bound to plasma proteins is 90%. The substance is metabolised to a high degree.

Less than 5% of the dose of the calcium antagonist is excreted unchanged in the urine. Up to 16% is excreted with the faeces. The elimination half-life is 3-6 hours. After oral administration in humans, verapamil is converted to the biologically active metabolite norverapamil. This active metabolite is about 20% as effective as the parent substance.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Maize Starch
Povidone
Microcrystalline Cellulose
Sodium Starch Glycolate
Colloidal Silica Anhydrous
Magnesium Stearate
Hypromellose
Hyprolose
Macrogol 6000
Titanium Dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Verap 40 tablets are packed in blisters of polypropylene and alufoil.

Pack size: 100 tablets, sample packs of 10 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 MARKETING AUTHORISATION HOLDER

Rowex Limited
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 711/16/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5th October 2001

Date of last renewal: 5th October 2006

10 DATE OF REVISION OF THE TEXT

October 2006