IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PA0711/185/001
Case No: 2070223

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

Previfect 20mg gastro-resistant tablets

the particulars of which are set out in 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 **28/01/2011** until **27/01/2016**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Previfect 20 mg gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 20 mg pantoprazole (as pantoprazole sodium sesquihydrate).

Excipient: contains 1µg of the colouring agent Ponceau 4R aluminium lake (E 124) per gastro-resistant tablet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet
A yellow, oval coated tablet imprinted **20** in black.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Short-term treatment of reflux symptoms (e. g. heartburn, acid regurgitation) in adults.

4.2 Posology and method of administration

Posology
The recommended dose is 20 mg pantoprazole (one tablet) per day.

It might be necessary to take the tablets for 2-3 consecutive days to achieve improvement of symptoms. Once complete relief of symptoms has occurred, treatment should be discontinued.
The treatment should not exceed 4 weeks without consulting a doctor.

If no symptom relief is obtained within 2 weeks of continuous treatment, the patient should be instructed to consult a doctor.

Special populations
No dose adjustment is necessary in elderly patients or in those with impaired renal or liver function.

Paediatric use
Previfect is not recommended for use in children and adolescents below 18 years of age due to insufficient data on safety and efficacy.

Method of administration
Previfect should not be chewed or crushed, and should be swallowed whole with liquid before a meal.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the other excipients (see section 6.1).

Co-administration with atazanavir (see section 4.5).

4.4 Special warnings and precautions for use

Patients should be instructed to consult a doctor if:

- They have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, persistent vomiting or vomiting with blood, since it may alleviate symptoms and delay diagnosis of a severe condition. In these cases, malignancy should be excluded.

- They have had previous gastric ulcer or gastrointestinal surgery.

- They are on continuous symptomatic treatment of indigestion or heartburn for 4 or more weeks.

- They have jaundice, hepatic impairment, or liver disease.

- They have any other serious disease affecting general well-being.

- They are aged over 55 years with new or recently changed symptoms.

Patients with long-term recurrent symptoms of indigestion or heartburn should see their doctor at regular intervals. Especially, patients over 55 years taking any non-prescription indigestion or heartburn remedy on a daily basis should inform their pharmacist or doctor.

Patients should not take another proton pump inhibitor or H_2 antagonist concomitantly.

Patients should consult their doctor before taking this medicinal product if they are due to have an endoscopy or urea breath test.

Patients should be advised that the tablets are not intended to provide immediate relief.
Patients may start to experience symptomatic relief after approximately one day of treatment with pantoprazole, but it might be necessary to take it for 7 days to achieve complete heartburn control. Patients should not take pantoprazole as a preventive medicinal product.

Decreased gastric acidity, due to any means - including proton pump inhibitors - increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing medicinal products leads to a slightly increased risk of gastrointestinal infections such as Salmonella, Campylobacter, or C. difficile.

This medicinal product contains the colouring agent Ponceau 4R aluminium lake, which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Previfect may reduce the absorption of active substances whose bioavailability is dependent on the gastric pH (e.g. ketoconazole).

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH-dependent. Therefore, pantoprazole must not be co-administered with atazanavir (see section 4.3).

Pantoprazole is metabolized in the liver via the cytochrome P450 enzyme system. An interaction of pantoprazole with other substances which are metabolized by the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline and an oral contraceptive containing levonorgestrel and ethinyl oestradiol.

Although no interaction during concomitant administration of phenprocoumon or warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in International Normalised Ratio (INR) have been

reported during concomitant treatment in the post-marketing period. Therefore, in patients treated with coumarin anticoagulants (e.g. phenprocoumon or warfarin), monitoring of prothrombin time/INR is recommended after initiation, termination or during irregular use of pantoprazole.

There were no interactions with concomitantly administered antacids.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of pantoprazole in pregnant women. Studies in animals have shown reproductive toxicity. Preclinical studies revealed no evidence of impaired fertility or teratogenic effects (see section 5.3). The potential risk for humans is unknown. This medicinal product should not be used during pregnancy.

Lactation
It is unknown whether pantoprazole is excreted in human breast milk. Animal studies have shown excretion of pantoprazole in breast milk. This medicinal product should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). If affected, patients should not drive or operate machines.

4.8 Undesirable effects

Approximately 5% of patients can be expected to experience adverse drug reactions (ADRs). The most commonly reported ADRs are diarrhoea and headache, both occuring in approximately 1% of patients. The following undesirable effects have been reported with pantoprazole.

Within the following table, undesirable effects are ranked under the following frequency classification:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1. Undesirable effects with pantoprazole in clinical trials and post-marketing experience

	Uncommon	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system			Thrombocytopenia Leukopenia	
Immune system disorders		Hypersensitivity (incl. anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders		Hyperlipidaemias and lipid increases (triglycerides, cholesterol); Weight chances		Hyponatraemia
Psychiatric disorders	Sleep disorders	Depression (and all aggravations)	Disorientation (and all aggravations)	Hallucinations; Confusion (especially in pre-disposed patients, as well as the aggravation of

				these symptoms in cases of pre-existence)
Nervous system disorders	Headache; Dizziness			
Eye disorders		Disturbances in vision / blurred vision		
Gastrointestinal disorders	Diarrhoea; Nausea / vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort			
Hepatobiliary disorders	Liver enzymes increased (transaminases, γ-GT)	Bilirubin increased		Hepatocellular injury; Jaundice; Hepatocellular failure
Skin and subcutaneous tissue disorders	Rash / exanthema / eruption; Pruritus	Urticaria; Angioedema		Stevens-Johnson syndrome; Lyell syndrome; Erythema multiforme; Photosensitivity
Musculoskeletal and connective tissue disorders		Arthralgia; Myalgia		
Renal and urinary disorders				Interstitial nephritis
General disorders and administration site conditions	Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral		

4.9 Overdose

There are no known symptoms of overdose in man.
Doses up to 240 mg administered intravenously over 2 minutes were well tolerated.
As pantoprazole is extensively protein bound, it is not readily dialysable.

In the case of overdose with clinical signs of intoxication, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton pump inhibitors, ATC code: A02BC02

Mechanism of action
Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific

blockade of the proton pumps of the parietal cells.

Pantoprazole is converted to its active form, a cyclic sulphenamide, in the acidic environment in the parietal cells where it inhibits the H+, K+-ATPase enzyme, i. e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. In most patients, freedom from heartburn and acid reflux symptoms is achieved in 1 week. Pantoprazole reduces acidity in the stomach and thereby increases gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the receptor level, it can inhibit hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the active substance is given orally or intravenously.

The fasting gastrin values increase under pantoprazole. On short-term use, in most cases they do not exceed the upper limit of normal. During long-term treatment, gastrin levels double in most cases. An excessive increase, however, occurs only in isolated cases. As a result, a mild to moderate increase in the number of specific endocrine (ECL) cells in the stomach is observed in a minority of cases during long-term treatment (simple to adenomatoid hyperplasia). However, according to the studies conducted so far, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids as were found in animal experiments (see section 5.3) have not been observed in humans.

Clinical efficacy
In a retrospective analysis of 17 studies in 5960 patients with gastro-oesophageal reflux disease (GORD) who were treated with 20 mg pantoprazole monotherapy, the symptoms associated with acid reflux e.g. heartburn and acid regurgitation were evaluated according to a standardised methodology. Studies selected had to have at least one acid reflux symptom recording point at 2 weeks. GORD diagnosis in these studies was based on endoscopic assessment, with the exception of one study in which the inclusion of the patients was based on symptomatology alone.

In these studies, the percentage of patients experiencing complete relief from heartburn after 7 days was between 54.0% and 80.6% in the pantoprazole group. After 14 and 28 days, complete heartburn relief was experienced in 62.9% to 88.6% and 68.1% to 92.3% of the patients, respectively.

For the complete relief from acid regurgitation, similar results were obtained as for heartburn. After 7 days the percentage of patients experiencing complete relief from acid regurgitation was between 61.5% and 84.4%, after 14 days between 67.7% and 90.4%, and after 28 days between 75.2% and 94.5%, respectively.

Pantoprazole was consistently shown to be superior to placebo and H2RA and non-inferior to other PPIs. Acid-reflux symptom relief rates were largely independent of the initial GORD stage.

5.2 Pharmacokinetic properties

Pharmacokinetics do not vary after single or repeated administration. In the dose range of 10 to 80 mg, the plasma kinetics of pantoprazole are linear after both oral and intravenous administration.

Absorption
Pantoprazole is completely and rapidly absorbed after oral administration. The absolute bioavailability from the tablet was found to be about 77 %. On average, at about 2.0 h - 2.5 h post administration (t_{max}) of a single 20 mg oral dose, the maximum serum concentrations (C_{max}) of about 1-1.5 µg/ml are achieved, and these values remain constant after multiple administration. Concomitant intake of food had no influence on bioavailability (AUC or C_{max}), but increased the variability of the lag-time (t_{lag}).

Distribution
Volume of distribution is about 0.15 l/kg and serum protein binding is about 98%.

Metabolism and excretion
Clearance is about 0.1 l/h/kg, and terminal half-life ($t_{1/2}$) about 1 h. There were a few cases of subjects with delayed elimination. Due to the specific binding of pantoprazole to the proton pumps within the parietal cell, the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).

Pantoprazole is almost exclusively metabolized in the liver. Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole; the rest is excreted with the faeces. The main metabolite in both serum and urine is desmethylpantoprazole, which is conjugated with sulphate. The half-life of the main metabolite (about 1.5 h) is not much longer than that of pantoprazole.

Special populations

Renal impairment
No dose reduction is recommended when pantoprazole is administered to patients with impaired renal function (including patients on dialysis, which removes only negligible amounts of pantoprazole). As with healthy subjects, the half-life of pantoprazole is short. Although the main metabolite has a longer half-life (2-3h), excretion is still rapid and thus accumulation does not occur.

Hepatic impairment
After administration of pantoprazole to patients with liver impairment (Child-Pugh classes A, B and C) the half-life values increased to between 3 and 7 h and the AUC values increased by a factor of 3-6, whereas the C_{max} only increased slightly by a factor of 1.3 compared with healthy subjects.

Elderly
The slight increase in AUC and C_{max} in elderly volunteers compared with younger subjects was not clinically relevant.

5.3 Preclinical safety data

Preclinical data reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

In the 2-year carcinogenicity studies in rats, neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the forestomach of rats in one study. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated and allows the conclusion that it is a secondary reaction to the massively elevated serum gastrin levels occurring in the rat during chronic high-dose treatment.

In the 2-year rodent studies an increased number of liver tumors was observed in rats (in one rat study only) and in female mice and was interpreted as being due to pantoprazole's high metabolic rate in the liver.
A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose (200 mg/kg) in one 2-year study. The occurrence of these neoplasms is associated with the pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. As the therapeutic dose in man is low, no side effects on the thyroid glands are expected.

In animal studies (rats) 5 mg/kg was the observed NOAEL (No Observed Adverse Effect Level) for embryotoxicity. Investigations revealed no evidence of impaired fertility or teratogenic effects.
Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentration of pantoprazole in the foetus is increased shortly before birth.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Calcium stearate
Cellulose microcrystalline
Crospovidone (type A)
Hydroxypropylcellulose (type EXF)
Sodium carbonate, anhydrous

Silica, colloidal anhydrous

Coating
Hypromellose
Iron oxide yellow (E 172)
Macrogol 400
Methacrylic acid – ethyl acrylate copolymer (1:1)
Polysorbate 80
Ponceau 4R aluminium lake (E 124)
Quinoline yellow aluminium lake (E 104)
Sodium lauryl sulphate
Titanium dioxide (E 171)
Triethyl citrate

Printing ink
Macrogol 600
Shellac
Povidone
Iron oxide black (E 172)
Iron oxide red (E 172)
Iron oxide yellow (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years
only for HDPE tablet containers:
Shelf life after first opening of the HDPE tablet container: 6 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Al-OPA/Al/PVC blister packaging: 7, 14 gastro-resistant tablets.
HDPE tablet container with polypropylene screw cap including a dessicant insert: 7, 14 gastro-resistant tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Bantry
Co Cork

8 MARKETING AUTHORISATION NUMBER

PA711/185/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th January 2011

10 DATE OF REVISION OF THE TEXT