IRISH MEDICINES BOARD ACT 1995, as amended

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

PA0436/041/002
Case No: 2072581

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

Norton Waterford

T/A IVAX Pharmaceuticals Ireland, **Unit 301**, **IDA Industrial Park**, **Cork Road, Waterford**, **Ireland**

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

Lanziop 30mg Gastro-resistant Capsules

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 **18/08/2010** until **10/11/2010**.

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

Lanziop 30mg Gastro-resistant Capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 30 mg of lansoprazole.
For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant capsule, hard.

White gelatin gastro-resistant capsule, filled with white to light brown or lightly pink coloured enteric-coated pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Treatment of duodenal or gastric ulcers, verified by endoscopy or radiography.
- Treatment of reflux oesophagitis.
- Long-term prophylaxis of reflux oesophagitis.
- Zollinger-Ellison syndrome.

4.2 Posology and method of administration

The capsules are swallowed whole with liquid. The capsules may be emptied, but the contents may not be chewed or ground.

Concomitant intake food slows down and reduces the absorption of lansoprazole. This medicine has the best effect when taken on an empty stomach. To achieve the optimal acid inhibitory effect, and hence most rapid healing and symptom relief, lansoprazole should be administered in the morning before food intake. When twice-daily dosage is needed the second dose should be administered in the evening before food intake.

Duodenal ulcer:
The recommended dose is 30 mg once daily for 2 weeks. In patients not fully healed within this time, the medication should be continued at the same dose for another 2 weeks.

Gastric ulcer:
The recommended dose is 30 mg once daily for 4 weeks. The ulcer usually heals within 4 weeks. In patients not fully healed within this time, the medication should be continued at the same dose for another 4 weeks.

Treatment of reflux oesophagitis:
The recommended dose is 30 mg once daily for 4 weeks. In patients not fully healed within this time, the treatment may be continued at the same dose for another 4 weeks.

Prophylaxis of reflux oesophagitis:
The recommended dose is 15 mg once daily. The dose may be increased up to 30 mg daily if necessary.

Zollinger-Ellison syndrome:
The recommended initial dose is 60 mg once daily. The dose should be individually adjusted and the treatment should be continued for as long as necessary. Daily doses of up to 180 mg have been used. If the required daily dose exceeds 120 mg, it should be given in two divided doses.

Hepatic and renal insufficiency:
There is no need to change the dose in patients with impaired renal function. However, the normal daily dose of 30 mg should not be exceeded in these patients. Care should be exercised in the administration of lansoprazole in patients with mildly to moderately impaired hepatic function. In mildly impaired patients, the dose should not exceed 30 mg. In patients with moderately impaired hepatic function, the dose should be restricted to 15 mg daily. Due to the lack of data in patients with severely impaired hepatic function, lansoprazole is not recommended in these patients

Children:
Lansoprazole is not recommended in children as safety and efficacy have not been established in this population.

Elderly:
Due to delayed elimination of lansoprazole in the elderly it may be necessary to administer the treatment in doses of 15–30 mg adjusted to individual requirements. However, the daily dose in the elderly should not exceed 30 mg.

4.3 Contraindications

Hypersensitivity to lansoprazole or to any of the excipents.

4.4 Special warnings and precautions for use

The diagnosis of gastroduodenal ulcers and reflux oesophagitis should be confirmed by endoscopy or other appropriate diagnostic means. Reflux oesophagitis may not present as ulceration and/or visual damage, therefore in certain cases endoscopy alone may not be sufficient.

The possibility of malign gastric tumours should be excluded before initiating treatment of gastric ulcers with lansoprazole because lansoprazole can mask the symptoms and delay the diagnosis.

Capsules of lansoprazole contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Lansoprazole should be used with caution in patients with hepatic dysfunction *(see Section 4.2, Posology and Method of Administration)*.

Lansoprazole has a similar mechanism of action to omeprazole and both increase gastric pH. The following statement is made by analogy to omeprazole. Decreased gastric acidity due to lansoprazole might be expected to increase gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with lansoprazole may lead to a slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

In patients suffering from gastro-duodenal ulcers, the possibility of *H. pylori* infection as an etiological factor should be considered.

If lansoprazole, in combination with antibiotics, is used for eradication therapy of *H.pylori*, then also instructions for the use of these antibiotics should also be followed.

Because of limited safety data for patients on maintenance treatment for longer than one year, regular review of the treatment and a thorough benefit-risk assessment should regularly be performed in these patients.

If visual disturbances occur during long-term use (>1 year), an ophthalmologist should be consulted.

Lansoprazole is not recommended in children as safety and efficacy have not been established in this population.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs associated with cytochrome P450
As lansoprazole is metabolised via a drug metabolising enzyme system associated with cytochrome P450 (CYP2C19 and CYP3A4), interactions with drugs metabolised via the same enzyme system are possible.

The effects of other drugs on lansoprazole

Drugs which inhibit CYP2C19
Drugs which inhibit CYP2C19 may increase the plasma concentration of lansoprazole. Fluvoxamine, an inhibitor of CYP2C19, increased the plasma concentrations of lansoprazole up to 4-fold.

Drugs which inhibit CYP3A4
Drugs which inhibit CYP3A4 such as ketoconazole, itraconazole, protease inhibitors, macrolides etc may markedly increase the plasma concentrations of lansoprazole.

Effects of lansoprazole on other drugs

Ketoconazole and itraconazole
The absorption of ketoconazole and itraconazole from the gastrointestinal tract is enhanced by the presence of gastric acid. Administration of lansoprazole may result in subtherapeutic concentrations of ketoconazole and itraconazole and the combination should be avoided. The effect may also be present if lansoprazole is combined with other drugs with pH-dependent absorption.

Digoxin
Coadministration of lansoprazole and digoxin may lead to increased digoxin plasma levels. In patients receiving digoxin, the plasma levels should therefore be monitored and the dose of digoxin adjusted if necessary.

Drugs metabolised by CYP3A4
Lansoprazole may give rise to increased plasma concentrations of drugs metabolised by CYP3A4. Caution is advised when combining lansoprazole with drugs which are metabolised by this enzyme.

Tacrolimus
Coadministration of lansoprazole increases the plasma concentrations of tacrolimus (a CYP3A and P-gp substrate). Lansoprazole exposure increased the mean exposure of tacrolimus by up to 81%. Monitoring of tacrolimus plasma concentrations is advised when concomitant treatment with lanzoprazole is initiated or ended.

Carbamazepine
Caution is advised during cotreatment with carbamazepine (a CYP3A substrate) and lansoprazole. This drug combination may result in increased carbamazepine concentrations as well as reduced lansoprazole concentrations.

Phenytoin
Studies have shown that the dosage of phenytoin (CYP2C19 and CYP2C9 substrate) may have to be reduced when administered concomitantly with lansoprazole. Caution and monitoring of phenytoin plasma concentrations is advised when initiating and ending lansoprazole treatment.

Warfarin
Caution and increased monitoring frequency is advised when initiating or ending lansoprazole cotreatment in patients treated with warfarin.

Theophyllin
Lansoprazole produces a 14% reduction in the plasma concentrations of theophylline. Individual patients may have a clinically relevant decrease. Caution is advised when combining the two drugs.

Clinically significant interactions of lansoprazole with nonsteroidal anti-inflammatory drugs or diazepam have not been demonstrated. Antacids and sucralfate may decrease the bioavailability of lansoprazole. The lansoprazole dose should therefore be taken at least an hour prior or after.

Lansoprazole has been observed to inhibit the transport protein P-glycoprotein (P-gp) *in vitro*. It may not be excluded that lansoprazole may affect transport via this protein giving rise to increased plasma concentrations of P-gp substrates such as digoxin.

Caution should be exercised when combining lansoprazole with drugs which have a narrow therapeutic index, as the effect of lansoprazole on the metabolism of other drugs has not been extensively investigated.

Therapy of *Helicobacter* pylori infection is intended to be combined, with concurrent administration of lansoprazole, clarithromycin and a further antibiotic. The influence of this combined administration has not yet been investigated systemically. For reasons of theoretical considerations, enhanced interactions with other medicinal products must be expected as a precaution. Monitoring of the serum levels of other medicinal products taken during the 1-week eradication therapy is therefore recommended. This concerns particularly such medicinal products also metabolised via the cytochrome P450 system.

The intake of food reduces the bioavailability of lansoprazole: it is recommended to take lansoprazole before the meal.

4.6 Pregnancy and lactation

For lansoprazole no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. The use of lansoprazole during pregnancy is not recommended.

It is not known whether lansoprazole is excreted in human breast milk. Animal studies have shown that lansoprazole is excreted in milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with lansoprazole should be made taking into account the benefit of breast-feeding to the child and the benefit of lansoprazole therapy to the woman.

4.7 Effects on ability to drive and use machines

Lansoprazole has minor or moderate influence on the ability to drive or operate machines.

Adverse drug reactions such as dizziness and fatigue may occur *(see section 4.8, Undesirable effects).* Under these conditions the ability to react may be decreased. This should be taken into account when driving or using machines.

4.8 Undesirable effects

	Common (>1%; <10%)	Uncommon (>0.1%; <1%)	Rare (>0.01%; <0.1%)	Very rare (<0.01%, including isolated reports)
Gastrointestinal	Nausea, diarrhoea, stomach ache, constipation, vomiting, flatulence and dyspepsia.		Dry mouth or throat, glossitis, candidiasis of the oesophagus, pancreatitis.	Colitis, stomatitis and black tongue.
Skin and hair	Eczema, urticaria**,** itching and rash.		Petechiae, purpura, hair loss, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.	
Nervous system	Headache, dizziness.		Restlessness, insomnia, drowsiness, depression, hallucinations, confusion, vertigo, paresthesia, somnolence and tremor.	
Liver and kidneys		Increase in liver enzyme levels.	Hepatitis or jaundice, icterus and interstitial nephritis.	
Blood			Thrombocytopenia, eosinophilia, pancytopenia and agranulocytosis, anemia and leucopenia.	
Cardiovascular			Peripheral edema, palpitations and chest pain.	
Musculoskeletal and connective tissue disorders			Muscle and joint pain.	
Senses			Taste disturbances and visual disturbances.	
Endocrine disorders				Gynecomastia, galactorrhoea.
General	Fatigue.		Fever, hyperhidrosis, bronchial constriction, impotence and angioedema.	Anaphylactic shock, general malaise.
Investigations				Increase in cholesterol and triglyceride levels.

4.9 Overdose

The effects of an overdose of lansoprazole in humans are not known (although the acute toxicity is likely to be low) and, consequently, instructions for treatment cannot be given. However, daily doses of up to 180 mg of lansoprazole have been administered in trials without significant undesirable effects.

Please refer to *section, 4.8. Undesirable effects* for possible symptoms of lansoprazole overdose.
Lansoprazole is not significantly eliminated by haemodialysis. If necessary, gastric emptying, administration of charcoal and symptomatic therapy are recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton pump inhibitors.
ATC-code: A02BC03.

Lansoprazole is a gastric proton pump inhibitor. It inhibits the final stage in the process of gastric acid formation by inhibiting the activity of the H+/K+ATPase of the parietal cells in the stomach. The inhibition is dose-dependent and reversible, and the effect applies to both basal and stimulated secretion of gastric acid. Lansoprazole is concentrated in parietal cells and becomes active in their acidic environment, whereupon it reacts with sulphydryl group of H+/K+ATPase causing inhibition of the enzyme activity.

Effect on gastric acid secretion:
Lansoprazole is a specific inhibitor of the parietal cell proton pump. A single oral dose of lansoprazole 30 mg inhibits pentagastrin-stimulated gastric acid secretion by about 80%. After repeated daily administration for seven days, about 90% inhibition of gastric acid secretion is achieved. It has a corresponding effect on the basal secretion of gastric acid. A single oral dose of 30 mg reduces basal secretion by about 70%; consequently, the patients' symptoms are relieved starting from the very first dose. After eight days of repeated administration the reduction is about 85%. A rapid relief of symptoms is obtained by 30 mg daily, and most patients with duodenal ulcer recover within 2 weeks; patients with gastric ulcer and reflux oesophagitis within 4 weeks.

5.2 Pharmacokinetic properties

Absorption and distribution:
Lansoprazole is rapidly inactivated by gastric acid and is consequently administered as enteric coated granules in gelatine capsules. Absorption from the duodenum is rapid and peak plasma concentration is achieved within 1.5–2 hours. Bioavailability after a single dose of 30 mg and after repeated daily administration is 80–90%. Intake of food slows the absorption rate of lansoprazole and reduces its bioavailability (AUC) by about 25%. Antacids and sucralfate may reduce the bioavailability of lansoprazole. The plasma protein binding of lansoprazole is about 95%, but this has not been found to have a significant effect on other protein-bound drugs.

Metabolism and elimination:
The metabolism of lansoprazole is mainly catalysed by the enzyme CYP2C19. The enzyme CYP3A4 also contributes to the metabolism. CYP2C19 is subject to genetic polymorphism and 2–6% of the population, called poor metabolisers (PMs), are homozygote for a mutant CYP2C19
allele and therefore lacks a functional CYP2C19 enzyme. The exposure to lansoprazole is several-fold higher in PMs than in extensive metabolisers (EMs).

The elimination half-life of lansoprazole is 1.0–2.0 hours. There is no change in half-life during treatment. A single dose of lansoprazole has an inhibitory effect on gastric acid secretion lasting more than 24 hours. Since lansoprazole is activated in the parietal cells, its plasma concentration is not related to gastric acid inhibition. Lansoprazole is mainly metabolised in the liver. Three metabolites have been identified in the plasma: the sulphone, 5-hydroxy lansoprazole and the sulphide. These metabolites have no significant effect on acid secretion. About 15–50% of the metabolites are secreted in the urine and the remainder in the faeces. Three metabolites have been identified in the urine: 5-hydroxy sulphone, 5-hydroxy sulphide and 5-hydroxy lansoprazole. In patients with cirrhosis the AUC of lansoprazole is significantly increased and the elimination half-life is prolonged, but no signs of accumulation of lansoprazole have been detected. The bioavailability of lansoprazole is not significantly changed in renal insufficiency. Elimination of lansoprazole in the elderly is slightly delayed.

5.3 Preclinical safety data

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

In two rat carcinogenicity studies, lansoprazole produced dose-related gastric ECL cell hyperplasia and ECL cell carcinoids associated with hypergastrinaemia due to inhibition of acid secretion. Intestinal metaplasia was also observed, as were Leydig cell hyperplasia and benign Leydig cell tumours. After 18 months of treatment retinal atrophy was observed. This was not seen in monkeys, dogs or mice.

In mouse carcinogenicity studies dose-related gastric ECL cell hyperplasia developed as well as liver tumours and adenoma of rete testis.

The clinical relevance of these findings is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sugar spheres (sucrose and maize starch)
Povidone
Disodium hydrogen phosphate dihydrate
Sodium laurilsulfate
Methacrylic acid-ethylacrylate copolymer (1:1) -dispersion 30 %
Talc
Macrogol 6000
Titanium dioxide (E171)
Polysorbate 80

Capsule shell:

Body:
Gelatin
Titanium dioxide(E171)

Cap:
Gelatin
Red iron oxide (15mg only) (E172)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

The shelf life after first opening the container is three months.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package.
Keep the container (bottle) tightly closed, in order to protect from moisture.

6.5 Nature and contents of container

Polyethylene (HDPE) plastic container with a polypropylene cap. The container contains a 2 g silica gel desiccant capsule.

Pack sizes: 14, 28, 56 and 98 capsules.
The 98 capsule container contains two (2x2 g) silica gel desiccant capsules.
Not all pack sizes will be marketed

Blister (laminated OPA/Al/PVC foil – aluminium foil)
Pack sizes of 14, 28, 56 and 98.

Not all pack sizes will be marketed.

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

Norton Waterford,
Trading as IVAX Pharmaceuticals Ireland
IDA Industrial Park,
Waterford,
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 0436/041/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 November 2005

10 DATE OF REVISION OF THE TEXT

August 2010