IRISH MEDICINES BOARD ACT 1995, as amended

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

PPA1500/055/001
Case No: 2083448

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

Profind Wholesale Ltd.

Unit 625, Kilshane Avenue, **Northwest Business Park**, **Dublin 15**, **Ireland**

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

Xyzal 5mg Film-coated 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 **28/07/2010**.

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

Xyzal 5mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5mg levocetirizine dihydrochloride.

Excipients: contains lactose monohydrate (63.5mg per tablet)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablet

Product imported from the UK:
White to off-white, oval, film-coated tablet with a Y logo on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) and chronic idiopathic urticaria.

4.2 Posology and method of administration

The film-coated tablet must be taken orally, swallowed whole with liquid and may be taken with or without food. It is recommended to take the daily dose in one single intake.

Adults and adolescents 12 years and above:
The daily recommended dose is 5 mg (1 film-coated tablet).

Elderly:
Adjustment of the dose is recommended in elderly patients with moderate to severe renal impairment (see Patients with renal impairment below).

Children aged 6 to 12 years:
The daily recommended dose is 5 mg (1 film-coated tablet).

For children aged 2 to 6 years no adjusted dosage is yet possible with the film-coated tablet formulation. It is recommended to use a paediatric formulation of levocetirine.

Patients with renal impairment:
The dosing intervals must be individualized according to renal function. Refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in ml/min is needed. The CLcr (ml/min) may be estimated from serum creatinine (mg/dl) determination using the following formula:

$$\frac{[140 - \textit{age(years)}] \times \textit{weight (kg)}}{72 \times \textit{serum creatinine (mg/dl)}} \quad (\times 0.85 \textit{ for women})$$

Dosing Adjustments for Patients with Impaired Renal Function:

Group	Creatinine clearance (ml/min)	Dosage and frequency
Normal	≥80	1 tablet once daily
Mild	50 – 79	1 tablet once daily
Moderate	30 – 49	1 tablet once every 2 days
Severe	< 30	1 tablet once every 3 days
End-stage renal disease - Patients undergoing dialysis	< 10-	Contra-indicated

In paediatric patients suffering from renal impairment, the dose will have to be adjusted on an individual basis taking into account the renal clearance of the patient and his body weight. There are no specific data for children with renal impairment.

Patients with hepatic impairment:
No dose adjustment is needed in patients with solely hepatic impairment. In patients with hepatic impairment and renal impairment, adjustment of the dose is recommended (see Patients with renal impairment above).

Duration of use:
Intermittent allergic rhinitis (symptoms <4 days/week or during less than 4 weeks) has to be treated according to the disease and its history; it can be stopped once the symptoms have disappeared and can be restarted again when the symptoms reappear. In case of persistent allergic rhinitis (symptoms >4days/week and during more than 4 weeks), continuous therapy can be proposed to the patient during the period of exposure to allergens. Clinical experience with 5 mg levocetirizine as a film-coated tablet formulation is currently available for a 6-month treatment period. For chronic urticaria and chronic allergic rhinitis, up to one year's clinical experience is available for the racemate.

4.3 Contraindications

Hypersensitivity to levocetirizine, to other piperazine derivatives, or to any of the excipients.

Patients with severe renal impairment at less than 10 ml/min creatinine clearance.

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

4.4 Special warnings and precautions for use

The use of the film coated tablet formulation is not recommended in children aged less than 6 years since this information does not allow for appropriate dose adaptation. It is recommended to use a paediatric formulation of levocetrine.

The administration of levocetirizine to infants and toddlers aged less than 2 years is not recommended.
Precaution is recommended with intake of alcohol (see Interactions).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with levocetirizine (including no studies with CYP3A4 inducers); studies with the racemate compound cetirizine demonstrated that there were no clinically relevant adverse interactions (with pseudoephedrine, cimetidine, ketoconazole, erythromycin, azithromycin, glipizide and diazepam). A small decrease in the clearance of cetirizine (16%) was observed in a multiple dose study with theophylline (400 mg once a day); while the disposition of theophylline was not altered by concomitant cetirizine administration.

The extent of absorption of levocetirizine is not reduced with food, although the rate of absorption is decreased.
In sensitive patients the simultaneous administration of cetirizine or levocetirizine and alcohol or other CNS depressants may have effects on the central nervous system, although it has been shown that the racemate cetirizine does not potentiate the effect of alcohol.

4.6 Pregnancy and lactation

For levocetirizine no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant or lactating women.

4.7 Effects on ability to drive and use machines

Comparative clinical trials have revealed no evidence that levocetirizine at the recommended dose impairs mental alertness, reactivity or the ability to drive. Nevertheless, some patients could experience somnolence, fatigue and asthenia under therapy with Xyzal. Therefore, patients intending to drive, engage in potentially hazardous activities or operate machinery should take their response to the medicinal product into account.

4.8 Undesirable effects

In therapeutic studies in women and men aged 12 to 71 years, 15.1% of the patients in the levocetirizine 5 mg group had at least one adverse drug reaction compared to 11.3% in the placebo group. 91.6 % of these adverse drug reactions were mild to moderate.
In therapeutic trials, the drop out rate due to adverse events was 1.0% (9/935) with levocetirizine 5 mg and 1.8% (14/771) with placebo.

Clinical therapeutic trials with levocetirizine included 935 subjects exposed to the drug at the recommended dose of 5 mg daily. From this pooling, following incidence of adverse drug reactions were reported at rates of 1 % or greater (common: >1/100, <1/10) under levocetirizine 5 mg or placebo:

Preferred Term (WHOART)	**Placebo (n =771)**	**Levocetirizine 5 mg (n = 935)**
Headache	25 (3.2 %)	24 (2.6 %)
Somnolence	11 (1.4 %)	49 (5.2 %)
Mouth dry	12 (1.6%)	24 (2.6%)
Fatigue	9 (1.2 %)	23 (2.5 %)

Further uncommon incidences of adverse reactions (uncommon >1/1000, <1/100) like asthenia or abdominal pain were observed.
The incidence of sedating adverse drug reactions such as somnolence, fatigue, and asthenia was altogether more common (8.1 %) under levocetirizine 5 mg than under placebo (3.1%).

In addition to the adverse reactions reported during clinical studies and listed above, very rare cases of the following adverse drug reactions have been reported in post-marketing experience.

- Immune system disorders: hypersensitivity including anaphylaxis
- Psychiatric disorders: aggression, agitation
- Nervous system disorders: convulsion
- Eyes disorders: visual disturbances
- Cardiac disorders: palpitations
- Respiratory, thoracic, and mediastinal disorders: dyspnoea
- Gastrointestinal disorders: nausea
- Hepatobiliary disorders: hepatitis
- Skin and subcutaneous tissue disorders: angioneurotic oedema, fixed drug eruption, pruritus, rash, urticaria
- Musculoskeletal, connective tissues, and bone disorders: myalgia
- Investigations: weight increased.

4.9 Overdose

a) Symptoms

Symptoms of overdose may include drowsiness in adults and initially agitation and restlessness, followed by drowsiness in children.

b) Management of overdoses

There is no known specific antidote to levocetirizine.
Should overdose occur, symptomatic or supportive treatment is recommended. Gastric lavage should be considered following short-term ingestion. Levocetirizine is not effectively removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihistamine for systemic use, piperazine derivative, ATC code: R06A E09.
Levocetirizine, the (R) enantiomer of cetirizine, is a potent and selective antagonist of peripheral H1-receptors.

Binding studies revealed that levocetirizine has high affinity for human H1-receptors (Ki = 3.2 nmol/l). Levocetirizine has an affinity 2-fold higher than that of cetirizine (Ki = 6.3 nmol/l). Levocetirizine dissociates from H1-receptors with a half-life of 115 ± 38 min.

After single administration, lrvocetirizine shows a receptor occupancy of 90% at 4 hours and 57% at 24 hours.

Pharmacodynamic studies in healthy volunteers demonstrate that, at half the dose, levocetirizine has comparable activity to cetirizine, both in the skin and in the nose.

The pharmacodynamic activity of levocetirizine has been studies in randomised, controlled trials:

In a study comparing the effects of levocetirizine 5mg, desloratadine 5mg, and placebo on histamine-induced wheal and flare, levocetirizine treatment resulted in significantly decreased wheal and flare formation, which lasted for 24 hours ($p<0.001$), compared with placebo and desloratadine.

The onset of action of levocetirizine 5 mg in controlling pollen-induced symptoms has been observed at 1 hours post drug intake in placebo controlled trials in the mdel of the allergen challenge chamber.

In vitro studies (Boyden chambers and cell layers techniques) show that levocetirizine inhibits eotaxin-induced eosinophil transendothelial migration through both dermal and lung cells. A pharmacodynamic experimental study *in vivo* (skin chamber technique) showed three main inhibitory effects of levocetirizine 5 mg in the first 6 hours of pollen-induced reaction, compared with placebo in 14 adult patients: inhibition of VCAM-1 release, modulation of vascular permeability and a decrease in eosinophil recruitment.

The efficacy and safety of levocetirizine has been demonstrated in several double-blind, placebo controlled, clinical trials performed in adult patients suffering from seasonal allergic rhinitis, perennial allergic rhinitis, or persistent allergic rhinitis. Levocetirizine has been shown to significantly improve symptoms of allergic rhinitis, including nasal obstruction in some studies.

A 6-month clinical study in 551 adult patients (including 276 levocetirizine-treated patients) suffering from persistent allergic rhinitis (symptoms present 4 days a week for at least 4 consecutive weeks) and sensitized to house dust mites and grass pollen demonstrated that levocetirizine 5 mg was clinically and statistically significantly more potent than placebo on the relief from the total symptom score of allergic rhinitis throughout the whole duration of the study, without any tachyphylaxis. During the whole duration of the study, levocetirizine significantly improved the quality of life of the patients.

The paediatric safety and efficacy of levocetirizine tablets has been studied in two placebo controlled clinical trials including patients aged 6-12 years and suffering from seasonal and perennial allergic rhinitis, respectively. In both trials, levocetirizine significantly improved symptoms and increased health-related quality of life.

In a placebo-controlled clinical trial including 166 patients suffering from chronic idiopathic urticaria, 85 patients were treated with placebo and 81 patients with levocetirizine 5mg once daily over six weeks. Treatment with levocetirizine resulted in significant decrease in pruritus severity over the first week and over the total treatment period as compared to placebo. Levocetirizine also resulted in a larger improvement of health-related quality of life as assessed by the Dermatology Life Quality Index as compared to placebo.

Pharmacokinetic / pharmacodynamic relationship:
The action on histamine-induced skin reactions is out of phase with the plasma concentrations.

ECGs did not show relevant effects of levocetirizine on QT interval.

5.2 Pharmacokinetic properties

The pharmacokinetics of levocetirizine are linear with dose- and time-independent with low inter-subject variability. The pharmacokinetic profile is the same when given as the single enantiomer or when given as cetirizine. No chiral inversion occurs during the process of absorption and elimination.

Absorption:
Levocetirizine is rapidly and extensively absorbed following oral administration. Peak plasma concentrations are achieved 0.9 h after dosing. Steady state is achieved after two days. Peak concentrations are typically 270 ng/ml and 308 ng/ml following a single and a repeated 5 mg o.d. dose, respectively. The extent of absorption is dose-independent and is not altered by food, but the peak concentration is reduced and delayed.

Distribution:
No tissue distribution data are available in humans, neither concerning the passage of levocetirizine through the blood-brain-barrier. In rats and dogs, the highest tissue levels are found in liver and kidneys, the lowest in the CNS compartment.
Levocetirizine is 90% bound to plasma proteins. The distribution of levocetirizine is restrictive, as the volume of distribution is 0.4 l/kg.

Biotransformation:
The extent of metabolism of levocetirizine in humans is less than 14% of the dose and therefore differences resulting from genetic polymorphism or concomitant intake of enzyme inhibitors are expected to be negligible. Metabolic pathways include aromatic oxidation, N- and O- dealkylation and taurine conjugation. Dealkylation pathways are primarily mediated by CYP 3A4 while aromatic oxidation involved multiple and/or unidentified CYP isoforms. Levocetirizine had no effect on the activities of CYP isoenzymes 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 at concentrations well above peak concentrations achieved following a 5 mg oral dose.
Due to its low metabolism and absence of metabolic inhibition potential, the interaction of levocetirizine with other substances, or vice-versa, is unlikely.

Elimination:
The plasma half-life in adults is 7.9 ± 1.9 hours. The mean apparent total body clearance is 0.63 ml/min/kg. The major route of excretion of levocetirizine and metabolites is via urine, accounting for a mean of 85.4% of the dose. Excretion via feces accounts for only 12.9% of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion.
Renal impairment:
The apparent body clearance of levocetirizine is correlated to the creatinine clearance. It is therefore recommended to adjust the dosing intervals of levocetirizine, based on creatinine clearance in patients with moderate and severe renal impairment. In anuric end stage renal disease subjects, the total body clearance is decreased by approximately 80% when compared to normal subjects. The amount of levocetirizine removed during a standard 4-hour hemodialysis procedure was < 10%.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Lactose monohydrate
Colloidal anhydrous silica
Magnesium stearate
Hypromellose (E464)
Titanium Dioxide (E171)
Macrogol 400

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

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

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Overlabelled cardboard carton containing three OPA/Aluminium/PVC blister strips (10 tablets per blister)

Pack size: 30 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

Profind Wholesale Ltd
Unit 625, Kilshane Avenue
Northwest Business Park
Dublin 15
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1500/55/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th June 2010

10 DATE OF REVISION OF THE TEXT

July 2010