IRISH MEDICINES BOARD ACT 1995, as amended

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

PPA1500/023/002
Case No: 2083742

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

Zantac 300mg 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

Zantac 300mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300mg of ranitidine (as hydrochloride).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Product imported from the UK:
White, round tablets engraved ‘GXEC3’ on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the treatment of duodenal ulcer and benign gastric ulcer including that associated with non-steroidal anti-inflammatory agents. Prevention of non-steroidal anti-inflammatory drug (including aspirin) associated duodenal ulcers, especially in patients with a history of peptic ulcer disease. Zantac Tablets are also indicated for treatment of post-operative ulcer, reflux oesophagitis, Zollinger-Ellison syndrome and other conditions where reduction of gastric acid secretion is likely to be beneficial.

4.2 Posology and method of administration

Adults:

The usual initial dosage is 150 mg bd or 300 nocte. This may be increased to ranitidine 300 mg twice daily without an increase incidence of unwanted effects. Subsequently a maintenance dose of 150 mg nocte may be used. Smoking is associated with a higher rate of ulcer relapse, and such patients should be advised to stop smoking. In those who fail to comply with such advice, a dose of 300 mg at night provides additional therapeutic benefit over the standard dose.

In most cases of duodenal ulcer, benign gastric ulcer and post operative ulcer, healing occurs within 4 weeks. Healing usually occurs after a further 4 weeks in those not fully healed after the initial 4 weeks. In ulcers following non-steroidal anti-inflammatory drug therapy, 8-12 weeks treatment may be necessary. For the prevention of non-steroidal anti-inflammatory drug associated duodenal ulcers ranitidine 150mg bd may be given concomitantly with non-steroidal anti-inflammatory drug therapy.

In the management of reflux oesophagitis the usual course of treatment is either 150 mg twice daily or 300 mg at night administered for up to a period of 8, or if necessary 12 weeks. In patients with moderate to severe oesophagitis the dose may be increased to 150 mg four times daily, alternatively 300 mg twice a day, if necessary.

For the long-term management of reflux oesophagitis, the recommended adult oral dose is 150mg twice daily for the prevention of relapse in patients with reflux oesophagitis. Zantac Tablets 150mg are not indicated in patients with complications of reflux oesophagitis e.g. severe oesophegeal stricture or Barratt's oesophagus.

In keeping with the recommended clinical practice it is advisable that patients on long-term maintenance therapy receive regular routine assessment by their practitioners.

In patients with Zollinger-Ellison syndrome the starting dose is 150 mg thrice daily, increased as necessary up to maximum of 6 grams daily.

In the prophylaxis of haemorrhage from stress ulceration in seriously ill patients or the prophylaxis of recurrent haemorrhage in patients bleeding from peptic ulceration, treatment with Zantac 150 mg twice daily may be substituted for Zantac Injection once oral feeding commences in patients considered to be still at risk from these conditions.

In obstetric patients on oral dose of 150 mg may be given at commencement of labour, followed by 150 mg at 6 hourly intervals. It is recommended that in addition, a non-particulate antacid (e.g. sodium citrate) should be given prior to induction of anaesthesia in any patients requiring emergency general anaesthesia.

Children:
The recommended oral dose for the treatment of peptic ulcer in children in 2 mg/kg to 4 mg/kg twice daily to a maximum of 300 mg ranitidine per day.

Renal insufficiency:
In patients with a creatinine clearance < 50 ml/min the usual dose is 150 mg nightly. In patients on dialysis, dosage should be given on completion of dialysis.

4.3 Contraindications

Use in patients known to have hypersensitivity to any component of the preparation.

4.4 Special warnings and precautions for use

Rare clinical reports suggest that ranitidine may precipitate acute porphyric attacks. Ranitidine should therefore be avoided in patients with a history of acute porphyria.

Before initiation of ranitidine treatment for any gastric ulceration, malignancy should be excluded by endoscopy and biopsy if possible. Treatment may mask the symptoms of malignancy, delaying diagnosis.

Ranitidine is excreted via the kidney and so plasma levels of the drug are increased in patients with severe renal impairment, adjust dosage detailed under section 4.2 above.

Regular supervision of patients who are taking non-steroidal anti-inflammatory drugs concomitantly with ranitidine is recommended, especially in the elderly and in those with a history of peptic ulcer.

In keeping with the recommended clinical practice it is advisable that patients on long-term maintenance therapy receive regular routine assessment by their practitioners.

4.5 Interaction with other medicinal products and other forms of interaction

Ranitidine, at blood levels produced by standard recommended doses, does not inhibit the hepatic cytochrome P450-linked mixed function oxygenase system. Accordingly, ranitidine in the usual therapeutic dose does not potentiate the actions of drugs which are inactivated by this enzyme; these include diazepam, lignocaine, phenytoin, propranolol, theophylline and warfarin.

4.6 Pregnancy and lactation

Ranitidine should not be administered during pregnancy or lactation unless considered essential by the physician. Ranitidine crosses the placenta and has been detected in breast milk.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

The following convention has been utilised for the classification of undesirable effects: very common (> 1/10), common (> 1/100, < 1/10), uncommon (> 1/1000, < 1/100), rare (> 1/10,000, < 1/1000), very rare (< 1/10,000).

Adverse event frequencies have been estimated from spontaneous reports from post-marketing data.

Blood & Lymphatic System Disorders
Very Rare: Blood count changes (leucopenia, thrombocytopenia). These are usually reversible. Agranulocytosis or pancytopenia, sometimes with marrow hypoplasia or marrow aplasia.

Immune System Disorders
Rare: Hypersensitivity reactions (urticaria, angioneurotic oedema, fever, bronchospasm, hypotension and chest pain).

Very Rare: Anaphylactic shock

These events have been reported after a single dose.

Psychiatric Disorders
Very Rare: Reversible mental confusion, depression and hallucinations.

These have been reported predominantly in severely ill and elderly patients.

Nervous System Disorders
Very Rare: Headache (sometimes severe),dizziness and reversible involuntary movement disorders.

Eye Disorders
Very Rare: Reversible blurred vision.

There have been reports of blurred vision, which is suggestive of a change in accommodation.

Cardiac Disorders
Very Rare: As with other H2 receptor antagonists bradycardia and A-V Block.

Vascular Disorders
Very Rare: Vasculitis.

Gastrointestinal Disorders
Very Rare: Acute pancreatitis. Diarrhoea.

Hepatobiliary Disorders
Rare: Transient and reversible changes in liver function tests.

Very Rare: Hepatitis (hepatocellular, hepatocanalicular or mixed) with or without jaundice, these were usually reversible.

Skin and Subcutaneous Tissue Disorders
Rare: Skin Rash.

Very Rare: Erythema multiforme, alopecia.

Musculoskeletal and Connective Tissue Disorders
Very Rare: Musculoskeletal symptoms such as arthralgia and myalgia.

Renal and Urinary Disorders
Very rare: Acute interstitial nephritis.

Reproductive System and Breast Disorders
Very Rare: Reversible impotence. Breast symptoms in men.

4.9 Overdose

Ranitidine is very specific in action and no particular problems are expected following overdosage with the drug. Symptomatic and supportive therapy should be given as appropriate. If need be, the drug may be removed from the plasma by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alimentary tract and metabolism.
ATC code: A02 BA02.

Zantac is a specific, rapidly acting histamine H2-antagonist. It inhibits basal and stimulated secretion of gastric acid, reducing both the volume and the acid and pepsin content of the secretion. Zantac has a relatively long duration of action and so a single 150mg dose effectively suppresses gastric acid secretion for twelve hours.

Although no clear casual link has been established, a large epidemiological study showed an increased risk of developing community acquired pneumonia in current users of H2 receptor antagonists versus those who had stopped treatment, with an observed adjusted relative risk increase of 1.63 (95% CI, 1.07 – 2.48). Therefore, in patients with conditions predisposing to the development of pneumonia, such as chronic lung disease, diabetes, or the immunocompromised, there may be an increased risk of developing community acquired pneumonia.

In patients such as the elderly, persons with chronic lung disease, diabetes of the immunocompromised, there may be an increased risk of developing community acquired pneumonia. A large epidemiological study showed an increased risk of developing community acquired pneumonia in current users of H2 receptor antagonists versus those who had stopped treatment, with an observed adjusted relative risk of 4.63 (95% CI, 1.07-2.48)

5.2 Pharmacokinetic properties

The bioavailability of ranitidine is consistently about 50%. Peak concentrations in plasma, normally in the range of 300-550 ng/ml, occur 2-3 hours after oral administration of a 150 mg dose. Concentrations of ranitidine in plasma are proportional to dose up to and including 300 mg.

Ranitidine is not extensively metabolised. Elimination of the drug is primarily by tubular secretion. The elimination half-life is 2-3 hours.

In balance studies with 150 mg ^{3}H-ranitidine 93% of an intravenous dose was excreted in urine and 5% in faeces; 60-70% of an oral dose was excreted in urine and 26% in faeces. Analysis of urine excreted in the first 24 hours after dosing showed that 70% of the intravenous dose and 35% of the oral dose were eliminated unchanged. The metabolism of ranitidine is similar after both oral and intravenous dosing; about 6% of the dose being excreted in urine as the N-oxide, 2% as the S-oxide, 2% as desmethylranitidine and 1-2% as the furoic acid analogue.

5.3 Preclinical safety data

Extensive studies have been carried out in animals. The pharmacology of ranitidine hydrochloride shows it to be a surmountable H2 receptor antagonist which produces an inhibition of gastric acid secretion. Extensive toxicological investigations have been conducted which predicted a very safe profile for clinical use. This safety has since been confirmed by extensive use in patients for many years.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Magnesium stearate
Croscarmellose sodium
Hypromellose
Titanium dioxide (E171)
Triacetin

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 as marketed in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Aluminium blister strips of 10 tablets contained in an over-labelled cardboard carton. Pack size 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

Any unused product or waste material should be disposed of in accordance with local requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

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

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1500/23/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th September 2009

10 DATE OF REVISION OF THE TEXT

July 2010