Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Kytril 1mg film-coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains l.0mg granisetron (as hydrochloride).

Excipients: Each tablet contains 69.38 mg lactose monohydrate

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Product imported from Italy:
White to almost-white, triangular, biconvex film-coated tablets marked 'K1' on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Kytril Tablets are indicated for the prevention of acute and delayed nausea and vomiting associated with cytostatic therapy.

4.2 Posology and method of administration

Posology
1 mg twice a day or 2 mg once a day for up to one week following radiotherapy or chemotherapy. The first dose of Kytril should be administered within 1 hour before the start of therapy. Dexamethasone has been used concomitantly at doses up to 20 mg once a day orally.

Paediatric population
The safety and efficacy of granisetron tablets in children have not yet been established.
No data are available.

Elderly and renal impairment
There are no special precautions required for its use in either elderly patients or those patients with renal or hepatic impairment.

Hepatic impairment
There is no evidence to date for an increased incidence of adverse events in patients with hepatic disorders. On the basis of its kinetics, whilst no dosage adjustment is necessary, granisetron should be used with a certain amount of caution in this patient group (see section 5.2).

Method of administration
The tablets should be swallowed whole with water.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

As granisetron may reduce lower bowel motility, patients with signs of sub-acute intestinal obstruction should be monitored following its administration.
As for other 5-HT_3 antagonists, ECG changes including QT interval prolongation have been reported with granisetron. In patients with pre-existing arrhythmias or cardiac conduction disorders this might lead to clinical consequences. Therefore caution should be exercised in patients with cardiac co-morbidities, on cardiotoxic chemotherapy and/or with concomitant electrolyte abnormalities (see section 4.5).
Cross-sensitivity between 5-HT_3 antagonists (e.g. dolasteron, ondansetron) has been reported.
Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Paediatric population
There is insufficient clinical evidence to recommend administration of these tablets to children.

4.5 Interaction with other medicinal products and other forms of interaction

As for other 5-HT_3 antagonists, cases of ECG modifications including QT prolongation have been reported with granisetron. In patients concurrently treated with medicinal products known to prolong QT interval and/or which are arrhythmogenic, this may lead to clinical consequences (see section 4.4).
In studies in healthy subjects, no evidence of any interaction has been indicated between granisetron and benzodiazepines (lorazepam), neuroleptics (haloperidol) or anti-ulcer medicinal products (cimetidine). Additionally, granisetron has not shown any apparent medicinal product interaction with emetogenic cancer chemotherapies.
No specific interaction studies have been conducted in anaesthetised patients.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is limited amount of data from the use of granisetron in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure**,** it is preferable to avoid the use of granisetron during pregnancy.

Breastfeeding
It is unknown whether granisetron or its metabolites are excreted in human milk. As a precautionary measure, breast-feeding should not be advised during treatment with Kytril.

Fertility
In rats, granisetron had no harmful effects on reproductive performance or fertility.

4.7 Effects on ability to drive and use machines

Kytril has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most frequently reported adverse reactions for Kytril are headache and constipation, which may be transient. ECG changes including QT prolongation have been reported with Kytril (see sections 4.4 and 4.5).

Tabulated list of adverse reactions
The following table of listed adverse reactions is derived from clinical trials and post-marketing data associated with Kytril and other 5-HT_3 antagonists.

Frequency catagories are as follows:

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)

Immune system disorders	
Uncommon	Hypersensitivity reactions e.g. anaphylaxis, urticaria
Psychiatric disorders	
Common	Insomnia
Nervous system disorders	
Very common	Headache
Uncommon	Extrapyramidal Reactions
Cardiac disorders	
Uncommon	QT prolongation
Gastrointestinal disorders	
Very common	Constipation
Common	Diarrhoea
Hepatobiliary disorders	
Common	Elevated hepatic transaminases*
Skin and subcutaneous tissue disorders	
Uncommon	Rash

*Occurred at a similar frequency in patients receiving comparator therapy

Description of selected adverse reactions
As for other 5-HT_3 antagonists, ECG changes including QT prolongation have been reported with granisetron (see sections 4.4 and 4.5).

4.9 Overdose

There is no specific antidote for Kytril. In the case of overdose with the tablets, symptomatic treatment should be given. Doses of up to 38.5 mg of Kytril as a single injection have been reported, with symptoms of mild headache but no other reported sequelae.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Kytril is a potent anti-emetic and highly selective antagonist of 5-hydroxytryptamine (5−HT_3) receptors. Radioligand binding studies have demonstrated that Kytril has negligible affinity for other receptor types including 5−HT and dopamine D_2 binding sites.

Kytril is effective intravenously, either prophylactically or by intervention, in abolishing the retching and vomiting evoked by administration of cytotoxic drugs or by whole body X−irradiation.

5.2 Pharmacokinetic properties

Pharmacokinetics of the oral administration is linear up to 2.5-fold of the recommended dose in adults. It is clear from the extensive dose-finding programme that the antiemetic efficacy is not unequivocally correlated with either administered doses or plasma concentrations of granisetron.

A fourfold increase in the initial prophylactic dose of granisetron made no difference in terms of either the proportion of patient responding to treatment or in the duration of symptoms control.

Absorption
Absorption of granisetron is rapid and complete, though oral bioavailability is reduced to about 60% as a result of first pass metabolism. Oral bioavailability is generally not influenced by food.

Distribution
Granisetron is extensively distributed, with a mean volume of distribution of approximately 3 l/kg. Plasma protein binding is approximately 65%.

Biotransformation
Granisetron is metabolized primarily in the liver by oxidation followed by conjugation. The major compounds are 7-OH-granisetron and its sulphate and glycuronide conjugates. Although antiemetic properties have been observed for 7-OH-granisetron and indazoline N-desmethyl granisetron, it is unlikely that these contribute significantly to the pharmacological activity of granisetron in man.
In vitro liver microsomal studies show that granisetron's major route of metabolism is inhibited by ketoconazole, suggestive of metabolism mediated by the cytochrome P-450 3A subfamily (see section 4.5).

Elimination
Clearance is predominantly by hepatic metabolism. Urinary excretion of unchanged Kytril averages 12% of dose whilst that of metabolites amounts to about 47% of dose. The remainder is excreted in faeces as metabolites. Mean plasma half-life in patients is approximately 9 hours, with a wide inter-subject variability.

Pharmacokinetics in special populations
Renal failure
In patients with severe renal failure, data indicate that pharmacokinetic parameters after a single intravenous dose are generally similar to those in normal subjects.

Hepatic impairment
In patients with hepatic impairment due to neoplasic liver involvement, total plasma clearance of an intravenous dose was approximately halved compared to patients without hepatic involvement.
Despite these changes, no dosage adjustment is necessary (see section 4.2).

Paediatric population
These tablets are not recommended in children.

Elderly patients
In elderly subjects after single intravenous doses, pharmacokinetic parameters were within the range found for non-elderly subjects.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, reproductive toxicity and genotoxicity. Carcinogenicity studies revealed no special hazard for humans when used in the recommended human dose. However, when administered in higher doses and over a prolonged period of time the risk of carcinogenicity cannot be ruled out.

A study in cloned human cardiac ion channels has shown that granisetron has the potential to affect cardiac repolarisation via blockade of HERG potassium channels. Granisetron has been shown to block both sodium and potassium channels, which potentially affects both depolarization and repolarization through prolongation of PR, QRS, and QT intervals. This data helps to clarify the molecular mechanisms by which some of the ECG changes (particularly QT and QRS prolongation) associated with this class of agents occur. However, there is no modification of the cardiac frequency, blood pressure or the ECG trace. If changes do occur, they are generally without clinical significance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose
Sodium Starch Glycolate
Hypromellose
Lactose Monohydrate
Magnesium Stearate
Titanium Dioxide (E171)
Macrogol 400
Polysorbate 80 (E433)

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

Over-labelled cardboard carton containing one aluminium foil blister (10 tablets per blister).
Pack size: 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 PARALLEL PRODUCT AUTHORISATION HOLDER

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

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1500/76/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th February 2011

10 DATE OF REVISION OF THE TEXT

October 2012