

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Kytril 2mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2mg granisetron (as the hydrochloride).

Excipients with known effect:

Each tablet contains 138.76 of lactose monohydrate

Sodium starch glycolate

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

The tablets are white to almost-white, triangular, biconvex tablets imprinted with 'K2' on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Kytril film-coated tablets are indicated in adults for the prevention and treatment of acute nausea and vomiting associated with chemotherapy and radiotherapy.

Kytril film-coated tablets are indicated in adults for prevention of delayed nausea and vomiting associated with chemotherapy and radiotherapy.

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.

Older people and renal impairment

There are no special precautions required for its use in either elderly patients or those patients with renal 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 listed in section 6.1.

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-HT₃ 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-HT₃ 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.

There have been reports of serotonin syndrome with the use of 5-HT₃ antagonists either alone, but mostly in combination with other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRIs), and serotonin noradrenaline reuptake inhibitors (SNRIs)). Appropriate observation of patients for serotonin syndrome-like symptoms is advised.

Kytril is essentially 'sodium free' as it contains less than 1 mmol sodium (23 mg) per dose (2 mg).

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 interactions

As for other 5-HT₃ 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.

Serotonergic medicinal products (e.g. SSRIs and SNRIs): there have been reports of serotonin syndrome following concomitant use of 5-HT₃ antagonists and other serotonergic medicinal products (including SSRIs and SNRIs) (see section 4.4).

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-HT₃ antagonists.

Frequency categories are as follows:

Very common: $\geq 1/10$;

Common $\geq 1/100$ to $< 1/10$;

Uncommon $\geq 1/1,000$ to $< 1/100$

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$)

Immune system disorders	
<i>Uncommon</i>	Hypersensitivity reactions e.g. anaphylaxis, urticaria
Psychiatric disorders	
<i>Common</i>	Insomnia
Nervous system disorders	
<i>Very common</i>	Headache
<i>Uncommon</i>	Extrapyramidal Reactions
<i>Uncommon</i>	Serotonin Syndrome (see also sections 4.4 and 4.5)
Cardiac disorders	
<i>Uncommon</i>	QT prolongation
Gastrointestinal disorders	
<i>Very common</i>	Constipation
<i>Common</i>	Diarrhoea
Hepatobiliary disorders	
<i>Common</i>	Elevated hepatic transaminases*
Skin and subcutaneous tissue disorders	
<i>Uncommon</i>	Rash

*Occurred at a similar frequency in patients receiving comparator therapy

Description of selected adverse reactions

As for other 5-HT₃ antagonists, ECG changes including QT prolongation have been reported with granisetron (see sections 4.4 and 4.5).

As with other 5-HT₃ antagonists, cases of serotonin syndrome (including altered mental status, autonomic dysfunction and neuromuscular abnormalities) have been reported following the concomitant use of Kytril and other serotonergic drugs (see sections 4.4 and 4.5).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to HPRC Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2. Tel: +353 1 6764971, Fax +353 1 6762517, website: www.hpra.ie, e-mail: medsafety@hpra.ie.

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

Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (5HT₃) antagonists.

ATC code: A04AA02.

Neurological mechanisms, serotonin-mediated nausea and vomiting

Serotonin is the main neurotransmitter responsible for emesis after chemo- or radio-therapy. The 5-HT₃ receptors are located in three sites: vagal nerve terminals in the gastrointestinal tract and chemoreceptor trigger zones located in the *area postrema* and the *nucleus tractus solitarius* of the vomiting center in the brainstem. The chemoreceptor trigger zones are located at the caudal end of the fourth ventricle (*area postrema*). This structure lacks an effective blood-brain barrier, and will detect emetic agents in both the systemic circulation and the cerebrospinal fluid. The vomiting centre is located in the brainstem medullary structures. It receives major inputs from the chemoreceptor trigger zones, and a vagal and sympathetic input from the gut. Following exposure to radiation or cytotoxic substances, serotonin (5-HT) is released from enterochromaffine cells in the small intestinal mucosa, which are adjacent to the vagal afferent neurons on which 5-HT₃ receptors are located. The released serotonin activates vagal neurons via the 5-HT₃ receptors which lead ultimately to a severe emetic response mediated via the chemoreceptor trigger zone within the *area postrema*.

Mechanism of action

Granisetron is a potent anti-emetic and highly selective antagonist of 5-hydroxytryptamine (5-HT₃) receptors. Radioligand binding studies have demonstrated that granisetron has negligible affinity for other receptor types including 5-HT and dopamine D₂ binding sites.

Chemotherapy- and radiotherapy-induced nausea and vomiting

Granisetron administered orally has been shown to prevent nausea and vomiting associated with cancer chemotherapy in adults.

Post-operative nausea and vomiting

Granisetron administered orally has been shown to be effective for prevention and treatment of post-operative nausea and vomiting in adults.

Pharmacological properties of granisetron

Interaction with neurotropic and other active substances through its activity on P 450-cytochrome has been reported (see section 4.5).

In vitro studies have shown that the cytochrome P450 sub-family 3A4 (involved in the metabolism of some of the main narcotic agents) is not modified by granisetron. Although ketaconazole was shown to inhibit the ring oxidation of granisetron *in vitro*, this action is not considered clinically relevant.

Although QT-prolongation has been observed with 5-HT₃ receptor antagonists (see section 4.4), this effect is of such occurrence and magnitude that it does not bear clinical significance in normal subjects. Nonetheless it is advisable to monitor both ECG and clinical abnormalities when treating patients concurrently with drugs known to prolong the QT (see section 4.5).

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 glucuronide 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 granisetron averages 12% of dose while that of metabolites amounts to about 47% of dose. The remainder is excreted in faeces as metabolites. Mean plasma half-life in patients by the oral and intravenous route 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 neoplastic 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.

Older people

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

Lactose monohydrate
Hypromellose
Sodium starch glycolate
Cellulose, microcrystalline
Magnesium stearate

Film-coat:
Hypromellose
Titanium dioxide (E171)
Macrogol 400
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Opaque PVC blisters sealed with an aluminium foil containing 2 or 10 tablets (1mg) or 1, 5 or 10 tablets (2mg).

Not all pack sizes may 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

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

7 MARKETING AUTHORISATION HOLDER

Atrahs Pharma Netherlands B.V.
Copenhagen Towers,
Ørestads Boulevard 108, 5.tv
DK-2300 København S,
Denmark

8 MARKETING AUTHORISATION NUMBER

PA22657/003/004

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