Australian Product Information - KYTRIL® (granisetron hydrochloride)

1. NAME OF THE MEDICINE

Granisetron hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

KYTRIL injections:

KYTRIL injection is available as an ampoule containing granisetron hydrochloride, equivalent to 3 mg of granisetron free base in 3 mL; and equivalent to 1 mg of granisetron free base in 1 mL.

KYTRIL tablets:

KYTRIL tablets contain granisetron hydrochloride (equivalent to 2 mg of granisetron free base).

KYTRIL tablets do not contain sucrose, gluten, tartrazine, or azo dyes.

Excipients with known effect: contains sugars as lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

KYTRIL tablet: white to almost white, triangular biconvex, film-coated tablet, debossed with "K2" on one face.

KYTRIL injection: sterile clear, colourless solution for injection.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Adults:

KYTRIL (tablets and injection) is indicated for use in adults for:

The prevention of nausea and vomiting induced by cytotoxic chemotherapy;

The prevention of nausea and vomiting induced by radiotherapy.

KYTRIL (injection) is also indicated for use in the treatment of nausea and vomiting induced by cytotoxic chemotherapy; and prevention and treatment of post-operative nausea and vomiting.

Paediatric:

KYTRIL injection is indicated for the prevention of nausea and vomiting induced by cytotoxic chemotherapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

Standard Dosage by presentation and indication for adult and paediatric patients are shown below.

Indication: Chemotherapy Induced Nausea and Vomiting (CINV)

Adults

Oral Administration

Prevention of nausea and vomiting in adults

The dose of KYTRIL is 2 mg once a day for up to one week following chemotherapy. The first dose of KYTRIL should be administered within 1 hour before the start of chemotherapy.

Treatment of established nausea and vomiting in adults

There is insufficient information to recommend the oral administration of KYTRIL in the treatment of CINV in adult patients.

Intravenous Administration

Prevention of nausea and vomiting in adults

A single dose of 3 mg of KYTRIL should be administered as an intravenous infusion, diluted in 20 to 50 mL infusion fluid and administered over 5 minutes prior to the start of chemotherapy. The infusion should be commenced within 30 minutes before the start of chemotherapy.

Prophylactic administration of KYTRIL should be completed prior to the start of chemotherapy.

In clinical trials, the majority of patients have required only a single dose of KYTRIL to control nausea and vomiting over 24 hours.

Treatment of established nausea and vomiting in adults

A single dose of 1 mg of KYTRIL should be administered as a 5 minute infusion. Further treatment doses of KYTRIL may be administered if required at least 10 minutes apart. The maximum dose of KYTRIL is 9 mg/24 hours.

In trials, patients have received a total dose of 160 µg/kg of intravenous KYTRIL in one day. There is also clinical experience in patients receiving a total of 600 µg/kg of intravenous KYTRIL over 5 days.

Paediatric

Oral Administration

There is insufficient information to recommend the oral administration of KYTRIL in the prevention or treatment of CINV in paediatric patients.

Intravenous Administration

Prevention of nausea and vomiting in paediatric patients

The recommended intravenous dose of KYTRIL in paediatric patients is 20 µg to 40 µg/kg body weight (up to 3 mg), which should be administered as an intravenous infusion, diluted in 10 to 30 mL infusion fluid and administered over 5 minutes, no more than 30 minutes before the start of chemotherapy.

Indication: Radiotherapy Induced Nausea and Vomiting

Adults

Oral Administration

Prevention of nausea and vomiting in adults

The dose of KYTRIL is 2 mg once a day, one hour before radiotherapy.

Intravenous Administration

Prevention of nausea and vomiting in adults

A single dose of 3 mg of KYTRIL should be administered as an intravenous infusion, diluted in 20 to 50 mL infusion fluid and administered over 5 minutes prior to the start of radiotherapy.

Treatment of nausea and vomiting in adults

There is insufficient information to recommend the intravenous administration of KYTRIL in the treatment of RINV in adult patients.

Paediatric

There is insufficient information to recommend the oral or intravenous administration of KYTRIL in the prevention or treatment of RINV in paediatric patients.

Indication: Post-operative Nausea and Vomiting

Adults

Oral Administration

Prevention and Treatment of Post-operative nausea and vomiting in adults

There is insufficient information to recommend the oral administration of KYTRIL in the prevention or treatment of Post-operative nausea and vomiting in adults.

Intravenous Administration

Prevention of post-operative nausea and vomiting in adults

A single dose of 1 mg of KYTRIL should be administered as a 30 second intravenous injection prior to induction of anaesthesia.

Treatment of established post-operative nausea and vomiting in adults

A single dose of 1 mg of KYTRIL should be administered by intravenous injection over 30 seconds.

Patients undergoing anaesthesia for elective surgery have received a total dose of 3 mg KYTRIL intravenous in one day.

Paediatric

There is insufficient information to recommend the oral or intravenous use of KYTRIL in the prevention or treatment of post-operative nausea and vomiting in paediatric patients.

Special Dosage Instructions

No dosage adjustment is required for the elderly, renally impaired or hepatically impaired (see Section 5.2 PHARMACOKINETIC PROPERTIES - Pharmacokinetics in Special Populations).

Combination with a Corticosteroid

The efficacy of IV or oral KYTRIL can be enhanced by the addition of an intravenous corticosteroid. For example, 8-20 mg of dexamethasone administered prior to the start of cytostatic therapy, or 250 mg methylprednisolone prior to the start of chemotherapy and again just after the end of chemotherapy.

Method of administration

Preparing the Infusion

Adults

To prepare the dose of 3 mg, withdraw 3 mL from the ampoule and dilute with a compatible infusion fluid to a total volume of 20 to 50 mL, in any of the following solutions: 0.9% sodium chloride, 0.18% sodium chloride and 4% glucose, 5% glucose, Hartmann's solution, 1.85% sodium lactate, mannitol.

Paediatric patients

To prepare the dose of 40 µg/kg, the appropriate volume is withdrawn (up to 3 mL from the ampoule) and diluted with infusion fluid (as for adults) to a total volume of 10 to 30 mL.

The injectable presentations contain no antimicrobial agent. Use once and discard any residue.

In order to reduce microbiological hazards it is recommended that the prepared infusion be commenced as soon as practicable after its preparation and should be completed within 24 hours. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

As a general precaution, KYTRIL should not be mixed in solution with other drugs other than dexamethasone sodium phosphate.

Admixtures of granisetron hydrochloride and dexamethasone sodium phosphate are compatible at concentrations of 10 to 60 µg/mL granisetron and 80 to 480 µg/mL dexamethasone phosphate in either 0.9% sodium chloride or 5% glucose intravenous infusion fluids. Stability data have been provided to demonstrate the physical and chemical stability of these solutions when stored at 25°C exposed to strong light for up to 24 hours. To reduce microbiological contamination hazards, it is recommended that admixing should be effected immediately prior to use and infusion commenced as soon as practicable after preparation. The admixture will have a shelf-life of 24 hours.

Parenteral drug products should be inspected visually for particulate matter and discolouration before administration whenever solution and container permit.

4.3 CONTRAINDICATIONS

KYTRIL is contraindicated in patients with known hypersensitivity to granisetron or to any of its excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As KYTRIL may reduce lower bowel motility, patients with signs of sub-acute intestinal obstruction should be monitored following administration of KYTRIL.

As with other 5-HT3 antagonists, cases of ECG modifications including QT prolongation have been reported with KYTRIL. The ECG changes with KYTRIL were minor, generally not of clinical significance and specifically, there was no evidence of proarrhythmia. However, 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 cardio-toxic chemotherapy and/or with concomitant electrolyte abnormalities.

In healthy subjects, no clinically relevant effects on resting EEG or on the performance of psychometric tests were observed after IV KYTRIL at any dose tested (up to 200 µg/kg).

Cross-sensitivity between 5-HT3 antagonists has been reported.

It is recommended that KYTRIL film-coated tablets are not taken by patients with the rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption.

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. If concomitant treatment with granisetron and other serotonergic drugs is clinically warranted, appropriate observation of the patient is advised (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Use in hepatic impairment

No special precautions are required for patients with hepatic impairment.

Use in renal impairment

No special precautions are required for patients with renal impairment.

Use in the elderly

No special precautions are required for the elderly.

Paediatric use

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

KYTRIL does not induce or inhibit the cytochrome P450 drug metabolising enzyme system in rodent studies. In humans, hepatic enzyme induction with phenobarbital resulted in an increase in total plasma clearance of intravenous KYTRIL of approximately one-quarter.

In healthy human subjects, KYTRIL has been safely administered with benzodiazepines, neuroleptics, and anti-ulcer medications commonly prescribed with anti-emetic treatments. Additionally, KYTRIL has shown no apparent drug interaction with emetogenic cancer chemotherapies.

No specific interaction studies have been conducted in anaesthetised patients, but KYTRIL has been safely administered with commonly used anaesthetic and analgesic agents. In addition, *in vitro* human microsomal studies have shown that the cytochrome P450 subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by KYTRIL.

As for other 5-HT3 antagonists, cases of ECG modifications including QT prolongation have been reported with KYTRIL. The ECG changes with KYTRIL were minor, generally not of clinical significance and specifically, there was no evidence of proarrhythmia. However, in patients concurrently treated with drugs known to prolong QT interval and/or are arrhythmogenic, this may lead to clinical consequences.

As with other 5-HT3 antagonists, cases of serotonin syndrome have been reported following the concomitant use of KYTRIL and other serotonergic drugs. If concomitant treatment with granisetron and other serotonergic drugs is clinically warranted, appropriate observation of the patient is advised (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

Category B1

There is no experience of granisetron in human pregnancy. Animal studies have shown no teratogenic effects in rats or rabbits at intravenous doses up to 9 and 3 mg/kg/day respectively, or at oral doses up to 125 and 32 mg/kg/day respectively. Time weighted systemic exposure (maternal plasma AUC) at the highest intravenous dose in rats was about 7 times higher than that in humans at therapeutic dose levels, but insufficient data are available for a similar comparison in rabbits. Because of the low safety margin indicated by the animal studies and because animal reproduction studies are not always predictive of human response, KYTRIL should be used during pregnancy only if clearly needed.

Use in lactation

A study in lactating rats showed that the rate of excretion in milk after IV dosing is less than 1% of the dose per hour, and that at least some of this is absorbed by the offspring.

There are no data on the excretion of granisetron in human breast milk, therefore use of the drug during lactation should be limited to situations where the potential benefit to the mother justifies the potential risk to the nursing infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no data on the effect of KYTRIL on the ability to drive, however there have been occasional reports of somnolence in clinical studies which should be taken into account.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

KYTRIL has been well tolerated in human studies. The most frequently reported adverse reactions for KYTRIL are headache and constipation which may be transient. ECD changes including QT prolongation have been reported with KYTRIL (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USEand Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

In patients receiving oral KYTRIL 1 mg b.d. for 1, 7 or 14 days, the following table lists adverse experiences reported in more than 5% of the patients with comparator and placebo incidences.

Table 1. Principal Adverse Events in Clinical Trials

Adverse Event	**Percent of Patients with an Event**		
	Oral KYTRIL[1] 1 mg b.d. (n=978)	**Comparator[2] (n=599)**	**Placebo (n=185)**
Headache[3]	21%	13%	12%
Constipation	18%	16%	9%
Asthenia	14%	10%	4%
Diarrhoea	8%	10%	4%
Abdominal pain	6%	6%	3%

1 Adverse events were recorded for 7 days when oral KYTRIL was given on a single day and for up to 28 days when oral KYTRIL was administered for 7 or 14 days.

2 Metoclopramide/dexamethasone; phenothiazines/dexamethasone; dexamethasone alone; prochlorperazine.

3 Usually mild to moderate in severity.

Table 2 gives the comparative frequencies of the five commonly reported adverse events (>3%) in patients receiving KYTRIL injection, 40 µg/kg, in single-day chemotherapy trials. These patients received chemotherapy, primarily cisplatin, and intravenous fluids during the 24-hour period following KYTRIL injection administration.

Table 2. Principal Adverse Events in Clinical Trials Single-Day Chemotherapy

Adverse Event	Percent of Patients with an Event	
	KYTRIL Injection[1] 40 µg/kg (n=1,268)	**Comparator[2] (n=422)**
Headache	14%	6%
Asthenia	5%	6%
Somnolence	4%	15%
Diarrhoea	4%	6%
Constipation	3%	3%

1 Adverse events were generally recorded over 7 days post-KYTRIL Injection administration.

2 Metoclopramide/dexamethasone and phenothiazines/dexamethasone.

In the absence of a placebo group, there is uncertainty as to how many of these events should be attributed to KYTRIL, except for headache, which was clearly more frequent than in comparison groups.

Adverse events reported in clinical trials other than those in the tables above are listed below. All adverse experiences are included in the list except those reported in terms so general as to be uninformative and those experiences for which the drug cause was remote. It should however be noted that causality has not necessarily been established.

Events are listed within body systems and categorised by frequency according to the following definitions: very common events reported at a frequency of greater or equal to 1/10 patients; common events reported at a frequency of greater or equal to 1/100 patients; uncommon events reported at a frequency of less than 1/100 but greater or equal to 1/1,000 patients; rare events reported at a frequency of less than 1/1,000 patients.

Body as a whole: *Common*: fever.

Cardiovascular: *Common*: hypertension; Uncommon: QT prolongation; Rare: hypotension, arrhythmias, sinus bradycardia, atrial fibrillation, varying degrees of A-V block, ventricular ectopy including non-sustained tachycardia, ECG abnormalities, angina pectoris, syncope.

Gastrointestinal disorders: *Very common*: Constipation.

Hypersensitivity: *Uncommon*: hypersensitivity reactions (e.g. anaphylaxis, shortness of breath, hypotension, urticaria).

Hepatic: *Common*: transient increases in AST and ALT. These are generally within the normal range and have been reported at similar frequency in patients receiving comparator therapy.

Nervous system: *Very common*: headache; *Common*: agitation, anxiety, CNS stimulation, dizziness, insomnia, somnolence; Uncommon: Serotonin Syndrome; Rare: extrapyramidal syndrome (only in presence of other drugs associated with this syndrome).

Dermatological: *Uncommon*: skin rashes.

Special Senses: *Common*: taste disorder.

Other common events often associated with chemotherapy also have been reported: leukopaenia, decreased appetite, anaemia, alopecia, thrombocytopaenia.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no specific antidote for KYTRIL. In the case of overdosage, symptomatic treatment should be given. Overdose with both the intravenous and oral formulations has occurred. Overdosage of up to 38.5 mg of KYTRIL as a single injection has been reported without symptoms or only the occurrence of a slight headache.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

KYTRIL is a potent antiemetic 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, alpha1 and alpha2, beta-adrenoreceptors, histamine H1, picrotoxin, benzodiazepine, opioid and dopamine D2 binding sites.

Antagonism of 5-HT3 receptors located peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone in the area postrema, is one of the most effective pharmacological methods of preventing cytotoxic-induced emesis. Mucosal enterochromaffin cells release serotonin during chemotherapy-induced emesis. Serotonin stimulates 5-HT3 receptors and evokes a vagal afferent discharge to subsequently induce emesis. Animal pharmacological studies have shown that in binding to 5-HT3 receptors, KYTRIL blocks serotonin stimulation, and is effective in alleviating the retching and vomiting evoked by cytostatic treatment. In the ferret animal model, a single KYTRIL injection prevented vomiting due to high-dose cisplatin or arrested vomiting within 5 to 30 seconds.

In healthy subjects, KYTRIL produced no consistent or clinically important changes in pulse rate, blood pressure or ECG. KYTRIL did not affect the plasma levels of prolactin or aldosterone.

KYTRIL injection showed no effect on gut transit time in normal volunteers given single doses up to 200 µg/kg. However, single and multiple doses of KYTRIL orally, slowed colonic transit time in normal volunteers.

Clinical trials

Intravenous Administration

Single-Day Chemotherapy

Cisplatin-Based Chemotherapy: In a double-blind, placebo-controlled study in 28 patients, KYTRIL Injection administered as a single intravenous infusion of 40 µg/kg, was significantly more effective than placebo in preventing nausea and vomiting induced by cisplatin chemotherapy.

KYTRIL Injection was also evaluated in a randomised dose response study of cancer patients receiving cisplatin >75 mg/m^2. Additional chemotherapeutic agents included: anthracyclines, carboplatin, cytostatic antibiotics, folic acid derivatives, methylhydralazine, nitrogen mustard analogs, podophyllotoxin derivatives, pyrimidine analogs and vinca alkaloids. KYTRIL Injection doses of 10 and 40 µg/kg were superior to 2 µg/kg in preventing cisplatin-induced nausea and vomiting.

Moderately Emetogenic Chemotherapy: KYTRIL Injection, 40 µg/kg, was compared with the combination of chlorpromazine (50 to 200 mg/24 hours) and dexamethasone (12 mg) in patients treated with moderately emetogenic chemotherapy, including primarily carboplatin >300 mg/m2, cisplatin 20 to 50 mg/m^2 and cyclophosphamide >600 mg/m^2. KYTRIL Injection was superior to the chlorpromazine/dexamethasone regimen in preventing nausea and vomiting.

Repeat Cycle Chemotherapy

In an uncontrolled trial, 75 cancer patients received KYTRIL Injection, 40 µg/kg prophylactically, for three cycles of chemotherapy. 31 patients received it for at least four cycles and 8 patients received it for at least six cycles. KYTRIL Injection efficacy remained relatively constant over the first six repeat cycles, with complete response rates (no vomiting and no moderate or severe nausea in 24 hours) of 65-70%. No patients were studied for more than 9 cycles.

During the clinical trial programme, there were 26 reports of cardiac arrest. Of these, 25 were considered to be unrelated to granisetron administration and were attributed to the underlying disease or concomitant cytostatic medication with time of onset up to 4 months after initiation of therapy.

In the one case where granisetron administration was causally related, the patient experienced cardiac arrest as part of a severe allergic reaction. This event was not related to any direct cardiotoxic effect of granisetron. A full recovery was made on discontinuation of therapy.

Of the 40 reports of renal failure, causality was assigned in 37 cases. All 37 were considered to be unrelated to granisetron administration and were attributed to the underlying disease or cisplatin, a known nephrotoxic agent.

Paediatric

KYTRIL injection 20 µg/kg was compared to chlorpromazine (0.5 mg/kg) plus dexamethasone (2 mg/m^2) in 88 paediatric patients treated with ifosfamide > 3 g/m^2 for two or three days. KYTRIL was administered on each day of ifosfamide treatment. At 24 hours, 22% of KYTRIL patients achieved complete response (no vomiting and no moderate or severe nausea in 24 hours) compared with 10% on the chlorpromazine/dexamethasone regimen. The median number of vomiting episodes was significantly lower in patients receiving granisetron than in patients receiving the combination of chlorpromazine/ dexamethasone (1.5 vs 7).

The efficacy and safety of intravenous doses of 10, 20 and 40 µg/kg were compared in 80 paediatric patients undergoing highly emetogenic chemotherapy. The median number of vomiting episodes were 2, 3, and 1 and the percentage of patients with no more than one vomiting episode were 48%, 42% and 56% respectively. There were no dose related safety issues.

KYTRIL administered intravenously has been shown to be effective in paediatric patients aged 2 years and above for the prevention of nausea and vomiting induced by cytotoxic chemotherapy. There is insufficient information to recommend intravenous administration of KYTRIL for the treatment of paediatric patients with nausea and vomiting induced by cytotoxic chemotherapy.

Radiotherapy

KYTRIL injection 3 mg was compared to a combination of intravenous (i.v.) metoclopramide (20 mg), dexamethasone (6 mg/m^2), and lorazepam (2 mg) in 30 patients to assess the efficacy and safety of KYTRIL for prophylaxis and control of radiotherapy induced emesis. The study drug was administered 1 hour before starting radiation therapy. The anti-emetic efficacy of KYTRIL was significantly more effective than the standard regimen of metoclopramide/dexamethasone/lorazepam in preventing radiotherapy induced emesis.

Very limited data are available on the use of KYTRIL in the treatment of nausea and vomiting induced by radiotherapy.

Post-operative nausea and vomiting

Prevention: KYTRIL injection 0.1 mg, 1.0 mg or 3.0 mg, was compared to placebo in a double-blind study to assess the efficacy and safety of KYTRIL in the prevention of post-operative nausea and vomiting (PONV) in 538 patients. KYTRIL was given as a 30 second injection prior to induction of anaesthesia. Patient groups receiving 1.0 mg and 3.0 mg KYTRIL responded significantly better than those in the 0.1 mg group.

Treatment: KYTRIL injection 0.1 mg, 1.0 mg or 3.0 mg, was compared to placebo in a double-blind study to assess the efficacy and safety of KYTRIL in 519 patients experiencing post-operative vomiting or severe nausea. In the 24 hour period after the day of surgery, patients receiving KYTRIL were less likely to experience nausea and vomiting than those receiving placebo.

Oral Administration

High Dose Cisplatin

KYTRIL 1.0 mg twice daily (b.d.) orally, for 7 days, was compared with the combination of metoclopramide (7 mg/kg) and dexamethasone (12 mg), followed by metoclopramide 10 mg three times daily (t.d.s) orally, for 6 days. 230 cancer patients received high dose cisplatin (mean dose 80 mg/m^2). Complete response rates (no vomiting, no more than mild nausea, no use of rescue therapy and not withdrawn from the study) at 24 hours were 52.1% for both treatment arms. Complete response rates at 7 days showed a trend in favour of granisetron (34.5% granisetron; 26.4% metoclopramide/ dexamethasone), but this difference did not reach statistical significance.

Moderately Emetogenic Chemotherapy

Oral doses of KYTRIL 0.25 mg to 2 mg b.d., for 7 days , were compared in a trial of 930 cancer patients receiving principally, cyclophosphamide, carboplatin and cisplatin (20 mg/m2 to 50 mg/m2). At 24 hours post-chemotherapy, all doses of KYTRIL were found to have anti-emetic efficacy with 1.0 mg being significantly better than 0.25 mg and 0.5 mg. 2.0 mg was not significantly better than 1.0 mg b.d. Results over the 7 day post chemotherapy period reflected those seen at 24 hours i.e. 1.0 mg b.d. was significantly superior to 0.25 mg or 0.5 mg b.d.

Combination with corticosteroid

Three studies demonstrated that in patients receiving chemotherapy, the addition of corticosteroids to prophylactic intravenous or oral KYTRIL resulted in significantly better control of nausea and vomiting over 24 hours. Doses of corticosteroid included 8-20 mg dexamethasone administered prior to the start of chemotherapy, or 250 mg methylprednisolone prior to the start of chemotherapy and again just after the end of chemotherapy. In one study an analysis of efficacy over seven days indicated that KYTRIL with dexamethasone was significantly more effective than KYTRIL alone.

Paediatric

There is insufficient information to recommend the oral administration of KYTRIL for the prevention or treatment of paediatric patients with nausea and vomiting induced by cytotoxic chemotherapy.

Radiotherapy

In a double-blind, parallel, placebo-controlled study, KYTRIL was found to be significantly more effective than placebo in the prevention of nausea and vomiting in 260 patients (from 38 centres), receiving at least 10 (maximum 20) fractions of upper abdominal radiation. The dose of KYTRIL administered in this study was 2 mg orally once daily, given one hour before radiation.

The proportion of patients without emesis and those without nausea for KYTRIL tablets, compared to placebo, was statistically significant ($P<0.0001$) at 24 hours after radiation, irrespective of the radiation dose. KYTRIL was significantly more effective than placebo in patients receiving up to 10 daily fractions of radiation, but was not significantly more effective than placebo in patients receiving 20 fractions.

Patients treated with KYTRIL tablets (n=134) had a significantly longer time to the first episode of vomiting (35 days vs. 9 days, $P<0.001$) relative to those patients who received placebo (n=126), and a significantly longer time to the first episode of nausea (11 days vs 1 day, $P<0.001$).

KYTRIL was well-tolerated, and no significant differences in unexpected or clinically significant adverse events were observed between the treatment groups.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

A linear pharmacokinetic relationship was found after oral administration of 2.5-fold the recommended dose and IV administration up to 4-fold the recommended dose.

Granisetron is rapidly and completely absorbed with peak plasma concentrations being reached at approximately 2 hours following oral administration. An accurate assessment of its oral bioavailability and the effect of food on its oral bioavailability is complicated by high intra-subject and inter-subject variability in pharmacokinetics. However, the bioavailability has been estimated by a variety of methods to be in the order of 60%.

Distribution

KYTRIL is extensively distributed with a mean volume of distribution of approximately 3 L/kg; plasma protein binding is approximately 65%, and granisetron distributes freely between plasma and red blood cells.

Metabolism

KYTRIL clearance is predominantly via hepatic metabolism and is rapid in most subjects. KYTRIL metabolism involves N-demethylation and aromatic ring oxidation followed by conjugation. Animal studies suggest some metabolites of granisetron may also have 5-HT3 receptor antagonist activity. However, in humans the metabolites are present in very low concentrations and are thought not to contribute to the pharmacological action.

Elimination

Mean plasma half-life of KYTRIL in patients is 9 hours with wide inter-subject variability. The plasma concentration of KYTRIL is not clearly correlated with antiemetic efficacy. Clinical benefit may be conferred even when granisetron is not detectable in plasma.

Urinary excretion of unchanged KYTRIL averages 12% of the dose in 48 hours, whilst the remainder is excreted as metabolites; 47% in the urine and 34% in the faeces.

Pharmacokinetics in Special Populations

Elderly: In elderly subjects after single intravenous doses, pharmacokinetic parameters were within the range found for younger healthy volunteers.

Renal Impairment: 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 clearance of KYTRIL was approximately halved compared to patients without hepatic impairment. However, no dosage adjustment is recommended.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Granisetron did not cause gene mutation in bacterial assays in *Salmonella* and *E. coli* or in a mouse lymphoma cell assay. No evidence of chromosomal damage was observed in human lymphocytes in vitro, or in a mouse micronucleus test. There was no evidence of DNA damage in assays of unscheduled DNA synthesis (UDS) in rat hepatocytes in vitro, or ex vivo. There was an apparent increase in UDS in HeLa cells exposed to granisetron in vitro when DNA synthesis was measured by scintillation counting of incorporated radioactive thymidine. However, when this test was repeated using a more definitive autoradiographic method, the test was negative for UDS. It is likely that the apparent UDS in the initial study was, in fact, a reflection of DNA synthesis in cells undergoing normal division (mitogenic activity).

Carcinogenicity

In a 24 month carcinogenicity study, mice were treated with granisetron in the diet at 1, 5 or 50 mg/kg/day. There was a statistically significant increase in the incidence of hepatocellular carcinomas in males and of hepatocellular adenomas in females dosed with 50 mg/kg/day. The incidence of hepatic tumours was not affected at 1 mg/kg/day.

In a 24 month carcinogenicity study, rats were treated with granisetron in the diet at 1, 5 or 50 mg/kg/day (reduced to 25 mg/kg/day at week 59 because of toxicity). Systemic exposure at the highest dose level was 1.7 times higher than that in humans at the recommended dose. There was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in males dosed with 5 mg/kg/day and above, and in females dosed with 50 mg/kg/day. No increase in liver tumours was observed in rats at a dose of 1 mg/kg/day in males and 5 mg/kg/day in females.

Experimental evidence in rats shows that granisetron exhibits the characteristics of a promoter of liver tumours with a clear no-effect dose of 1 mg/kg. The probable mechanism for this effect is sustained liver cell hyperplasia. In a study in which rats were treated for 12 months with 100 mg/kg/day, the observed promoting effects were reversible upon cessation of treatment. Additionally, there was no adverse effect on the liver of dogs treated orally for 12 months with granisetron 5 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

KYTRIL Tablets

microcrystalline cellulose,

sodium starch glycollate,

hypromellose,

lactose monohydrate,

magnesium stearate

Film-coating

hypromellose,

macrogol 400,

polysorbate 80,

titanium dioxide.

KYTRIL Injection

sodium chloride 0.9%,

water for injections,

citric acid monohydrate,

sodium hydroxide,

hydrochloric acid

6.2 INCOMPATIBILITIES

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION- Method of administration.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION- Method of administration, for storage times for prepared infusion solutions

6.4 SPECIAL PRECAUTIONS FOR STORAGE

KYTRIL tablets should be stored below 30°C.

KYTRIL ampoules should be stored below 30°C and protected from direct sunlight.

Ampoules removed from the pack should be stored protected from light.

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION- Method of administration, for precautions regarding the storage of admixtures and prepared infusion solutions.

6.5 NATURE AND CONTENTS OF CONTAINER

KYTRIL tablets: opaque PVC/Al blister packs of 1 or 5.

KYTRIL injection: 3 mg/3 mL, pack of 1 clear glass ampoule; 1 mg/1mL, pack of 5 clear glass ampoules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

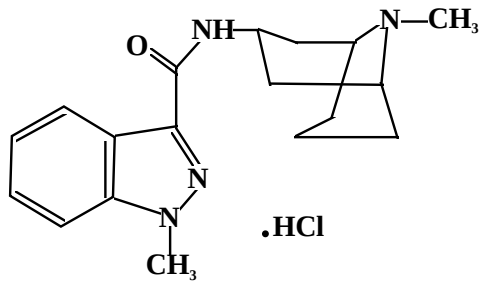
The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

6.7 PHYSICOCHEMICAL PROPERTIES

Granisetron hydrochloride is a white to off-white crystalline solid with a bitter taste, which is freely soluble in water and 0.9% sodium chloride at 20°C.

The systematic chemical name is endo-N-(9-methyl-9-azabicyclo [3.3.1] non-3-yl)-1-methyl-1H-indazole-3-carboxamide hydrochloride. The molecular weight of the salt is 348.9 and that of the base is 312.4.

Chemical structure



CAS number

107007-99-0

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription only medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

5 August 1997

10. DATE OF REVISION

22 April 2021

Summary table of changes

Section changed	Summary of new information
All	Reformat
6.1	Update ingredient to AAN