PRODUCT MONOGRAPH

Pr KYTRIL®

Granisetron Hydrochloride Tablets
1 mg & 2 mg granisetron as hydrochloride

Granisetron Hydrochloride Injection
1 mg/mL granisetron as hydrochloride, 1 mL and 4 mL vials

Antiemetic
(5-HT_3 receptor antagonist)

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PrKYTRIL®

Granisetron Hydrochloride Tablets

Granisetron Hydrochloride Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
oral	tablets, 1 mg and 2 mg	hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, sodium starch glycollate and Opadry® YS-1-18027-A (hypromellose, titanium dioxide, macrogol 400, and polysorbate 80). CONTAINS LACTOSE
i. v. injection	1 mL and 4 mL vials, 1 mg/mL injection	sodium chloride, benzyl alcohol, citric acid monohydrate, water for injection and hydrochloric acid and/or sodium hydroxide for pH adjustment. CONTAINS BENZYL ALCOHOL

INDICATIONS AND CLINICAL USES

KYTRIL (granisetron hydrochloride) is indicated for:

Adults

- The prevention of nausea and vomiting associated with emetogenic cancer chemotherapy, including high dose cisplatin;
- The prevention of nausea and vomiting associated with radiation, including total body irradiation and fractionated abdominal radiation;
- The prevention and treatment of postoperative nausea and vomiting. As with other antiemetics, routine prophylaxis is not recommended in patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients

where nausea and/or vomiting must be avoided during the postoperative period, KYTRIL Injection is recommended even where the incidence of postoperative nausea and/or vomiting is low.

Geriatrics (>65 years of age)

Chemotherapy-induced and Radiation-induced Nausea and Vomiting

Safety and efficacy of KYTRIL appear to be similar to that observed in younger adults (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Post-Operative Nausea and Vomiting

Clinical experience in the use of KYTRIL in the prevention and treatment of post-operative nausea and vomiting is limited and it is not indicated for use in this population (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Pediatrics

Safety and efficacy of KYTRIL has not been adequately studied in children or adolescents under 18 years of age and it is not indicated for use in this population (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

- KYTRIL (granisetron hydrochloride) is contraindicated in patients with a known hypersensitivity to the drug or to any component of its formulations.

WARNINGS AND PRECAUTIONS

Carcinogenesis and Mutagenesis

KYTRIL (granisetron hydrochloride) has been associated with an increased occurrence of hepatocellular tumours in carcinogenicity studies performed in rodents at doses in excess of the recommended human dose. Although the clinical significance of these findings has not been determined, the use of this drug should be restricted to the treatment of nausea and vomiting in patients undergoing emetogenic cancer chemotherapy. The recommended dosage of KYTRIL should not be exceeded.

Granisetron was administered to rats in the diet in a 24 month carcinogenicity study. The incidence of hepatocellular carcinomas and adenomas was significantly increased in male rats treated at doses of 5 mg/kg/day and in rats of both sexes treated with 25 mg/kg/day. No increase in the rate of occurrence of liver tumours was observed in the 1 mg/kg/day treatment group (100 times the recommended human dose given intravenously).

In another 24 month carcinogenicity study, mice were administered granisetron in the diet at doses of 1, 5, and 50 mg/kg/day. There was a statistically significant increase in the incidence of

hepatocellular carcinomas in males and hepatocellular adenomas in females dosed with 50 mg/kg/day. No statistically significant increase in liver tumours was observed in mice at a dose of 5 mg/kg/day (500 times the recommended human dose given intravenously).

Cardiovascular

As for other 5-HT_3 antagonists, cases of ECG modifications including QT prolongation have been reported with KYTRIL. These ECG changes with KYTRIL were minor and generally not of clinical significance, specifically with 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. See also DRUG INTERACTIONS and ADVERSE REACTIONS, Post-marketing Reports of Adverse Events.

Gastrointestinal

KYTRIL is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction. The use of KYTRIL in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distention. Patients with signs of sub-acute intestinal obstruction should be monitored following administration of KYTRIL.

Sensitivity/Resistance

Hypersensitivity reactions may occur in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists.

Special Populations

Pregnant Women: The use of KYTRIL in pregnant women has not been studied and is not recommended. Reproduction studies performed in pregnant rats given granisetron at intravenous dosages up to 9 mg/kg/day and pregnant rabbits at intravenous dosage up to 3 mg/kg/day revealed no evidence of impaired fertility or harm to the fetus due to granisetron (see TOXICOLOGY, Reproduction).

Nursing Women: It is not known whether granisetron is excreted in human milk. Nursing is not recommended during treatment with KYTRIL.

Pediatrics: The safety and efficacy of KYTRIL has not been adequately studied in children or adolescents under 18 years of age (see INDICATIONS AND CLINICAL USES and DOSAGE AND ADMINISTRATION).

Geriatrics (> *65* years of age):

During clinical trials, 713 patients 65 years of age or older received intravenous KYTRIL and of 325 patients 65 years of age or older who received oral KYTRIL, 298 were 65 to 74 years of age and 27 were 75 years of age or older. The efficacy and safety of KYTRIL did not appear to be age dependent (see INDICATIONS AND CLINICAL USES and DOSAGE AND ADMINISTRATION).

During postoperative nausea and vomiting clinical trials, 168 patients 65 years of age or older, of which 47 were 75 years of age or older, received KYTRIL Injection. Clinical studies of KYTRIL Injection did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients (see INDICATIONS AND CLINICAL USES and DOSAGE AND ADMINISTRATION).

Information for Patients

Effect on Ability to Drive and Use Machinery

In healthy subjects, no clinically relevant effects on resting EEG or on the performance of psychometric tests were observed after i.v. KYTRIL at any dose tested (up to 200 mcg/kg). There are no data on the effect of KYTRIL on the ability to drive. As there have been occasional reports of somnolence in clinical studies, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that the drug treatment does not affect them adversely.

ADVERSE REACTIONS

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Drug Reaction Overview

The most common adverse events reported by patients receiving intravenous or oral KYTRIL in single-day chemotherapy trials are: headache, asthenia, somnolence, diarrhea, constipation, and abdominal pain (see Table 1 for the percentages of patients with these events). The only two common adverse experiences recognized to be causally related to KYTRIL are constipation and headache.

As for other 5-HT_3 antagonists, cases of ECG modifications including QT prolongation have been reported with KYTRIL. These ECG changes with KYTRIL were minor and generally not of clinical significance, specifically with no evidence of proarrhythmia (see WARNINGS AND PRECAUTIONS, Cardiovascular, DRUG INTERACTIONS, and ADVERSE REACTIONS, Post-marketing Reports of Adverse Events).

Clinical Trial Adverse Drug Reactions

Chemotherapy-induced Nausea and Vomiting
Intravenous KYTRIL was given as a single dose. Oral KYTRIL was given either as a single dose or divided dose for 1, 7, or 14 days. Patients received cancer chemotherapy which consisted primarily of cisplatin or cyclophosphamide regimens. During the 24-hour period following intravenous administration of KYTRIL, I.V. fluids were also given. Adverse events were recorded over seven days when KYTRIL was given on a single day and up to 28 days when KYTRIL was administered for 7 or 14 days. In the absence of a placebo group, the relationship of observed adverse events to treatment with KYTRIL is difficult to judge.

Table 1 gives the frequencies of the six adverse events most commonly reported by patients receiving intravenous or oral KYTRIL in single-day chemotherapy trials. This table does not include those events that are commonly associated with chemotherapy or the underlying malignant disease.

Table 1. Principal Adverse Events in Clinical Trials of Single-Day Chemotherapy

	Percentage of Patients with Event Intravenous KYTRIL (10-40 mcg/kg) (n=1519)	Percentage of Patients with Event Oral KYTRIL (1.0 mg b.i.d. or 2.0 mg u.i.d.) (n=1322)
Headache	14%	22%
Asthenia	5%	15%
Somnolence	4%	2%
Diarrhea	5%	8%
Constipation	4%	17%
Abdominal Pain	3%	6%

The only two common adverse experiences recognized to be causally related to KYTRIL are constipation and headache. As with other drugs of this class, rare cases of hypersensitivity reactions, sometimes severe (e.g. anaphylaxis, shortness of breath, hypotension, urticaria) have been reported.

Radiation-induced Nausea and Vomiting
In controlled clinical trials, the adverse events reported by patients receiving KYTRIL Tablets and concurrent radiation were similar to those reported by patients receiving KYTRIL Tablets prior to chemotherapy. The most frequently reported adverse events were diarrhea (25.6%), asthenia (22.0%) and constipation (15.5%). Headache (7.7%), however, was less prevalent in this patient population. Table 2 lists the adverse experiences (>5%) in patients who received KYTRIL Tablets or placebo.

Table 2. Principal Adverse Events in Clinical Trials- RINV

	Percentage of Patients with Event Oral KYTRIL 1.0 mg b.i.d. (n=134)	Percentage of Patients with Event Placebo (n=128)
Diarrhea	28%	34%
Asthenia	25%	20%
Constipation	19%	5%
Abdominal Pain	11%	9%
Nausea (after 20 radiation fractions)	11%	9%
Decreased appetite	10%	7%
Pain	8%	4%
Headache	5%	11%

Postoperative Nausea and Vomiting

The adverse events listed in Table 3 were reported in ≥ 2% of adults receiving KYTRIL Injection 1 mg during controlled clinical trials.

Table 3. Adverse Events ≥ 2%

	Percent of Patients With Event	
	KYTRIL Injection 1 mg (n=267)	**Placebo (n=266)**
Pain	10.1	8.3
Constipation	9.4	12.0
Anemia	9.4	10.2
Headache	8.6	7.1
Fever	7.9	4.5
Abdominal Pain	6	6.0
Hepatic Enzymes Increased	5.6	4.1
Insomnia	4.9	6.0
Bradycardia	4.5	5.3
Dizziness	4.1	3.4
Leukocytosis	3.7	4.1
Anxiety	3.4	3.8
Hypotension	3.4	3.8
Diarrhea	3.4	1.1
Flatulence	3	3
Infection	3	2.3
Dyspepsia	3	1.9
Hypertension	2.6	4.1
Urinary Tract Infection	2.6	3.4
Oliguria	2.2	1.5
Coughing	2.2	1.1

In a clinical study conducted in Japan, the types of adverse events differed notably from those reported in Table 3. The adverse events in the Japanese study that occurred in ≥ 2% of patients

and were more frequent with KYTRIL 1 mg than with placebo were: fever (56% to 50%), sputum increased (2.7% to 1.7%), and dermatitis (2.7% to 0%).

Less Common Clinical Trial Adverse Drug Reactions (≤1%)

Chemotherapy-induced Nausea and Vomiting

The safety profile of KYTRIL has been evaluated in 3269 patients receiving intravenous KYTRIL (2 to 160 mcg/kg) and 2,600 patients receiving oral KYTRIL (0.25 - 20 mg) in single-day and multiple-day clinical trials with emetogenic cancer therapies. In the listings which follow, a COSTART-based dictionary terminology has been used to classify reported adverse experiences. The frequencies presented, therefore, represent the proportion of the patients who experienced an event of the type cited on at least one occasion while receiving KYTRIL.

Experiences are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions:

frequent experiences are defined as: those occurring on one or more occasion in at least 1/100 patients

infrequent adverse experiences as: those occurring in less than 1/100 but at least 1/1000 patients

rare experiences as: those occurring in less than 1/1000 patients

Many adverse experiences are observed in cancer chemotherapy patients. All adverse experiences are included except those for which the drug cause was remote, those reported in terms so general as to be uninformative and those already listed in Table 1.

Body As A Whole:	**Frequent:** Abdominal pain **Infrequent:** Abdomen enlarged, chills, fever, malaise **Rare:** Allergic reaction, chest pain
Cardiovascular System:	**Infrequent:** Hypertension, hypotension, migraine, syncope, vasodilatation **Rare:** Arrhythmia, bradycardia, palpitation, postural hypotension, tachycardia, ventricular arrhythmia, angina pectoris, and atrial fibrillation
Gastrointestinal System:	**Frequent:** Decreased appetite **Infrequent:** Dry mouth, dyspepsia, flatulence, jaundice, liver function tests abnormal [Elevation of AST and ALT (>2 times the upper limit of normal)], nausea **Rare:** Gastrointestinal haemorrhage, hepatic coma, ileus, liver damage, melena, vomiting
Hemic and Lymphatic System:	**Rare:** Coagulation time increased, eosinophilia, leukopenia, anemia, thrombocytopenia
Metabolic and Nutritional:	**Infrequent:** Hypokalemia **Rare:** Bilirubinemia, edema, hyperphosphatemia, hyponatremia
Nervous System:	**Infrequent:** Agitation, anxiety, dizziness, drugged feeling, insomnia, nervousness, paresthesia, tremor **Rare:** Coma, depersonalisation, grand mal convulsion, vertigo

Respiratory System:	**Infrequent:** Dyspnea, hiccup **Rare:** Epistaxis, rhinitis, sinusitis
Skin and Appendages:	**Infrequent:** Pruritus, rash, sweating **Rare:** Photosensitivity
Special Searches:	**Rare:** Puncture site pain
Special Senses:	**Infrequent:** Taste perversion **Rare:** Abnormal vision
Urogenital System:	**Infrequent:** Dysuria **Rare:** Urinary incontinence

Post-marketing Reports of Adverse Events

The post-marketing safety experience in over 4 million patients is consistent with the clinical trial safety information.

Cases of cardiac arrest, ventricular fibrillation, ventricular tachycardia, ECG QT prolonged, sudden death and syncope were reported rarely in post-marketing experience. Some reports showed temporal association with granisetron, most of them also presenting confounding factors such as concomitant medications, medical history, and/or known risk factors. The relationship to granisetron cannot be established or excluded, either as an effect of the drug alone or in combination with other factors (see WARNINGS AND PRECAUTIONS, Cardiovascular, and DRUG INTERACTIONS).

DRUG INTERACTIONS

Overview

No pharmacodynamic interaction was found between single 160 mcg/kg i.v. doses of granisetron and single oral doses of 2.5 mg lorazepam or 3 mg haloperidol. Pharmacokinetic interactions with these drugs were not investigated.

The pharmacokinetic characteristics of a single 40 mcg/kg i.v. dose of granisetron were not significantly different whether it was administered alone or following 8 days of treatment with the hepatic enzyme inhibitor, cimetidine (200 mg q.i.d.).

Granisetron does not induce or inhibit the cytochrome P_{450} drug metabolizing enzyme system.

As for other 5-HT_3 antagonists, cases of ECG modifications including QT prolongation have been reported with KYTRIL. These ECG changes with KYTRIL were minor and generally not of clinical significance, specifically with 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.

DOSAGE AND ADMINISTRATION

Recommended Dose, Dosage Adjustment and Administration

Emetogenic Chemotherapy
Adults:
Injection:
The recommended dosage of KYTRIL is 10 mcg/kg infused intravenously over 5 minutes, beginning within 30 minutes before initiation of chemotherapy only on the day(s) when chemotherapy is given (see Reconstitution for dilution instructions).

Oral:
The recommended dosage of oral KYTRIL is 2 mg on the day of chemotherapy. This may be administered either as a single dose (2 x 1 mg or 1x 2 mg) one hour before chemotherapy or as a divided dose of 1 mg one hour before chemotherapy followed by a second 1 mg dose 12 hours post-chemotherapy. The need for additional doses beyond 24 hours post-chemotherapy has not been investigated.

Geriatrics: Available clinical data suggest that dosage reductions may not be necessary in this patient population (see INDICATIONS AND CLINICAL USES and WARNINGS AND PRECAUTIONS).

Pediatrics: See INDICATIONS AND CLINICAL USES and WARNINGS AND PRECAUTIONS.

Renally impaired patients: Available clinical data suggest that dosage reductions may not be necessary in this patient population.

Hepatically impaired patients: The clearance of KYTRIL is reduced by half in patients with hepatic impairment. The dose response of KYTRIL in patients with hepatic impairment has not been determined.

Radiation (either Total Irradiation or Fractionated Abdominal Radiation)
Adults:
Oral:
The recommended adult dosage of oral KYTRIL is 2 mg once daily. 2 x 1 mg or 1 x 2 mg tablets are taken one hour before radiation.

Geriatrics: Available clinical data suggest that dosage reductions may not be necessary in this patient population (see INDICATIONS AND CLINICAL USES and WARNINGS AND PRECAUTIONS).

Pediatrics: See INDICATIONS AND CLINICAL USES and WARNINGS AND PRECAUTIONS.

Prevention and Treatment of Postoperative Nausea and Vomiting
Adults:
Injection:

The recommended dosage for prevention of postoperative nausea and vomiting is 1 mg of KYTRIL, undiluted, administered intravenously over 30 seconds, before induction of anesthesia or immediately before reversal of anesthesia.

The recommended dosage for the treatment of nausea and/or vomiting after surgery is 1 mg of KYTRIL, undiluted, administered intravenously over 30 seconds.

Geriatrics: Clinical experience in the use of KYTRIL in the prevention and treatment of post-operative nausea and vomiting is limited and it is not indicated for use in this population (see INDICATIONS AND CLINICAL USES and WARNINGS AND PRECAUTIONS).

Pediatrics: See INDICATIONS AND CLINICAL USES and WARNINGS AND PRECAUTIONS.

Reconstitution:
Diluted Solutions
Infusion Preparation:

To prepare granisetron hydrochloride injection for i.v. infusion, aseptically transfer the appropriate amount of granisetron hydrochloride injection to the desired volume of any of the following solutions: 0.9% sodium chloride, 0.18% sodium chloride and 4% dextrose, 5% dextrose, Hartmann's solution, sodium lactate, mannitol (see STORAGE AND STABILITY section).

OVERDOSAGE

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

KYTRIL (granisetron hydrochloride) is a selective antagonist of 5-hydroxytryptamine (5-HT_3) receptors. Following exposure to emetogenic cancer chemotherapy, mucosal enterochromaffin cells release serotonin which stimulates 5-HT_3 receptors located peripherally on vagal nerve terminals and centrally in the nucleus tractus solitarus. The antiemetic effect of granisetron appears to involve antagonism of the serotonin-induced stimulation of vagal afferent activity.

Radioligand binding studies have demonstrated that KYTRIL has negligible affinity for other 5-HT receptors or for dopamine D_2 receptor binding sites.

Pharmacodynamics

In healthy subjects, KYTRIL produced no consistent or clinically significant changes in pulse rate, blood pressure or ECG. There was no evidence of an effect on psychomotor performance at intravenous doses of up to 200 mcg/kg i.v. KYTRIL did not affect the plasma levels of prolactin or aldosterone at single intravenous doses of up to 300 mcg/kg or after repeat intravenous doses of 40 mcg/kg for 5.5 days.

Following single and multiple oral doses, KYTRIL slowed colonic transit in normal volunteers.

Pharmacokinetics

Chemotherapy-Induced Nausea and Vomiting

Injection:

In adult cancer patients undergoing chemotherapy and in healthy volunteers, infusion of a single 40 mcg/kg dose of KYTRIL produced the following mean pharmacokinetic data:

Table 4. Pharmacokinetic Parameters in Adult Cancer Patients Undergoing Chemotherapy and in Volunteers, Following a Single Intravenous 40 mcg/kg Dose of KYTRIL (granisetron hydrochloride) Injection

	Peak Plasma Concentration (ng/mL)	Terminal Phase Plasma Half-Life (h)	AUC (ng•h/mL)	Total Clearance (L/h)
Cancer Patients (N=14)				
Mean	63.8*	8.95*	167*	25.8*
Range	18.0 to 176	0.90 to 31.1	26.0 to 294	8.92 to 95.2
Young Adult Volunteers 21 to 42 years (N=20)				
Mean	64.3+	4.91+	89.7+	51.8+
Range	11.2 to 182	0.88 to 15.2	15.6 to 201	11.3 to 176
Elderly Volunteers 65 to 81 years (N=20)				
Mean	57.0+	7.69+	115+	27.1+
Range	14.6 to 153	2.65 to 17.7	37.7 to 240	10.9 to 58.4

* 5 minute infusion + 3 minute infusion

Oral:

In healthy volunteers and adult cancer patients undergoing chemotherapy, administration of oral KYTRIL produced the following mean pharmacokinetic data:

Table 5. Pharmacokinetic Parameters (Mean [range]) In Adult Cancer Patients Undergoing Chemotherapy and in Volunteers Following Oral KYTRIL (granisetron hydrochloride)

	Peak Plasma Concentration (ng/mL)	Terminal Plasma Half-Life (h)	Area Under Curve (ng•h/mL)	Total Clearance (L/h)
Cancer Patients 1.0 mg, b.i.d., 7 days (n=24)	8.19 [1.97 to 18.4]	N.D.*	54.2 [10.2 to 126]	34.1 [7.94 - 98.0]
Volunteers single dose (n=25)				
1.0 mg	4.10 [0.58 to 7.37]	8.74 [2.40 to 19.9]	43.7 [2.85 to 142]	53.3 [7.04 to 351]
2.5 mg	9.44 [1.68 to 19.5]	7.24 [2.54 to 17.0]	105 [7.75 to 319]	67.2 [7.84 to 323]

* Not determined after oral administration.

Distribution: KYTRIL is extensively distributed between plasma and red blood cells with a mean volume of distribution of approximately 3 L/kg. Plasma protein binding is approximately 65%.

Metabolism: The clearance of granisetron occurs predominantly through hepatic metabolism. Biotransformation pathways involve N-demethylation and aromatic ring oxidation followed by conjugation.

Excretion: In normal volunteers, the urinary excretion of unchanged KYTRIL averages 12% of the administered dose over a period of 48 hours, while the remainder of the dose is excreted as metabolites, 47% in the urine and 34% in the feces. The metabolism of granisetron involves N-demethylation and aromatic ring oxidation followed by conjugation.

Postoperative Nausea and Vomiting

Injection

In adult patients (age range, 18 to 64 years) recovering from elective surgery and receiving general anesthesia, mean pharmacokinetic data obtained from a single 1 mg dose of KYTRIL administered intravenously over 30 seconds are shown in Table 6.

Table 6. Pharmacokinetic Parameters in 16 Adult Surgical Patients Following a Single Intravenous 1 mg Dose of KYTRIL (granisetron hydrochloride) Injection

	Peak Plasma Concentration (ng/mL)	Terminal Plasma Half-Life (h)	Area Under Curve (ng•h/mL)	Total Clearance (L/h)
Mean	75.5	8.63	72.2	19.1
Range	16.8-187	1.77-17.73	21.0-137	7.30-47.6

The pharmacokinetics of granisetron in patients undergoing surgery were similar to those seen in cancer patients undergoing chemotherapy.

Special Populations and Conditions

Pediatrics: The safety and efficacy of KYTRIL has not been adequately studied in children or adolescents under 18 years of age.

Geriatrics: In geriatric (mean age 71 yrs) subjects after single intravenous doses of 40 mcg/kg, pharmacokinetic parameters were within the range found for young subjects (mean age 29 yrs). Although the elimination half-life was prolonged and the total plasma clearance reduced in the geriatric relative to the young subject group, no significant differences were determined between the two groups with regard to maximum plasma concentration or area under the plasma concentration time curve values (see Table 4).

Gender/Race: There were too few male and Black patients to adequately assess differences in effect in either population (see CLINICAL TRIALS section).

Hepatic Insufficiency: A pharmacokinetic study in patients with hepatic impairment due to neoplastic liver involvement showed that total clearance was approximately halved and mean area under the plasma concentration time curve (AUC) values were approximately doubled compared to patients without hepatic impairment.

Renal Insufficiency: Although renal clearance was decreased in subjects with severe renal impairment (N=11) relative to normal volunteers (N=12), total plasma clearance was numerically higher in this renally impaired group (43 L/h) than in the normal volunteers (32 L/h). Mean area under the plasma concentration time curve values were similar for the two subject groups.

Cancer Patients: Following intravenous administration, mean terminal elimination half-life values are approximately twice as long in cancer patients as they are in healthy adult volunteers, while clearance values are decreased by approximately 50% (see Table 4). Available data do not

allow a formal comparison of elimination half-life or clearance between volunteers and cancer patients receiving oral KYTRIL.

STORAGE AND STABILITY

Vials should be stored between 15 - 30°C. Protect from light. Once the vial is penetrated, its contents should be used within 30 days. Discard unused portion.

Store tablets at controlled room temperature (15 - 30°C).

KYTRIL has been shown to be stable for at least 24 hours in the following solutions: 0.9% sodium chloride, 0.18% sodium chloride and 4% dextrose, 5% dextrose, Hartmann's solution, sodium lactate, mannitol when stored at ambient temperature in normal indoor illumination (natural daylight supplemented by fluorescent light). As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Appropriate precautions should be taken to maintain the sterility of the infusion solution once prepared.

Pharmaceutical Precautions:
As a general precaution, KYTRIL should not be mixed in solution with other drugs.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition

Injection:
Each mL contains 1 mg granisetron as hydrochloride, 0.9% sodium chloride, 1.0% benzyl alcohol, 0.2% citric acid monohydrate, water for injection and hydrochloric acid and/or sodium hydroxide for pH adjustment.

Tablets for oral administration:

1 mg Tablet: each white, triangular, biconvex, film-coated KYTRIL tablet, debossed with "K1" on one face, contains granisetron hydrochloride equivalent to granisetron, 1 mg.

2 mg Tablets: each white, triangular, biconvex, film-coated KYTRIL tablet, debossed with "K2" on one face, contains granisetron hydrochloride equivalent to granisetron, 2 mg.

Inactive ingredients are: hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, sodium starch glycollate and Opadry® YS-1-18027-A (hypromellose, titanium dioxide, macrogol 400, and polysorbate 80).

Packaging

Injection:

KYTRIL (granisetron hydrochloride) is supplied in clear glass multi-use vials of 1 mL or 4 mL, packaged in boxes of 1 vial. Each vial contains 1 mg/mL granisetron as hydrochloride.

Tablets for oral administration:

KYTRIL 1 mg tablets are packaged in blister cards of 2 or 10 tablets.

KYTRIL 2 mg tablets are packaged in blister cards of 1 tablet or 5 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

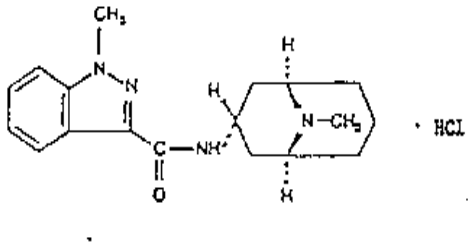
Drug Substance

Proper name: Granisetron Hydrochloride

Chemical name: 1-methyl-N-(9-methyl-endo-9-azabicyclo[3.3.1] non-3-yl)-1H-indazole-3-carboxamide, monohydrochloride.

Molecular formula and molecular mass: Hydrochloride Salt: $C_{18}H_{24}N_4O.HCl$, 348.9
Free base: $C_{18}H_{24}N_4O$, 312.4

Structural formula:



Physicochemical properties: Granisetron hydrochloride is a white to off-white cohesive solid with a bitter taste. At 20°C, granisetron hydrochloride is freely soluble in water and 0.9% sodium chloride. All analytical methods used to test granisetron hydrochloride indicated that batches were all of the same crystal form and there were no additional polymorphs. The pH of a 1% aqueous solution is in the range of 4.0 - 6.5. The melting point of granisetron hydrochloride is 295°C - 300°C with decomposition.

CLINICAL TRIALS

Chemotherapy-Induced Nausea and Vomiting:

Injection:
KYTRIL has been shown to prevent nausea and vomiting associated with single-day and repeat-cycle cancer chemotherapy.

Single-Day Chemotherapy
In a double-blind, placebo-controlled study in 28 cancer patients, KYTRIL administered as a single intravenous infusion of 40 mcg/kg, was significantly more effective than placebo in preventing nausea and vomiting induced by cisplatin chemotherapy (see Table 7).

Table 7. Prevention of Chemotherapy-Induced Nausea and Vomiting - Single-Day Cisplatin Therapy[1]

	KYTRIL	Placebo	P value
Number of Patients	14	14	
Response Over 24 Hours			
Complete Response[2]	93%	7%	<0.001
No Vomiting	93%	14%	<0.001
No More Than Mild Nausea	93%	7%	<0.001

1 Cisplatin administration began within 10 minutes of KYTRIL infusion and continued for 1.5 to 3.0 hours. Mean cisplatin doses were 86 mg/m^2 in the group of patients treated with KYTRIL and 80 mg/m^2 in the placebo group.

2 No vomiting and no moderate or severe nausea.

KYTRIL was evaluated in a double-blind, randomized dose response study of 353 patients stratified for high (> 80 to 120 mg/m^2) or low (50 to 79 mg/ m^2) cisplatin dose. Response rates of patients for both cisplatin strata are given in Table 8.

Table 8. Prevention of Chemotherapy-Induced Nausea and Vomiting - Single-Day High-Dose and Low-Dose Cisplatin Therapy[1]

Dose of KYTRIL (mcg/kg)	5	10	20	40
Number of Patients	82	90	88	93
Complete Response[2] (%)	23	48*	48*	44*
No Vomiting (%)	32	54*	53*	48*
No Nausea (%)	22	46*	38*	38*

1 Cisplatin administration began within 10 minutes of KYTRIL infusion and continued 2 hours (mean). Mean cisplatin dose was 82 mg/m^2.

2 No vomiting and no rescue medication.

* p<0.05 vs 5 mcg/kg.

The 10, 20 and 40 mcg/kg doses were more effective than the 5 mcg/kg dose in preventing nausea and vomiting within 24 hours of chemotherapy administration. The 10 mcg/kg dose was at least as effective as the higher doses.

Repeat Cycle Chemotherapy

Two single blind, active-controlled studies have been performed in which KYTRIL was administered to a total of 246 chemotherapy-naive patients with malignant disease receiving cytostatic therapy (≥15 mg/m^2/day cisplatin, ≥1.2 g/m^2/day ifosfamide, and ≥120 mg/m^2 /day etoposide) for 5 days. KYTRIL was administered as a daily 40 mcg/kg i.v. dose 5 min. before the infusion of the cytostatic with up to two additional 40 mcg/kg i.v. doses permitted over each 24 hr period. In both studies, response rates (percentage of patients with no vomiting and no more than mild nausea in the 24 hour period following administration of KYTRIL) were observed to decline with repeated treatment, decreasing from 87-90% at day 1 to 70-71% at day 3, and 67-73% at day 5.

Co-Administration with Dexamethasone

A randomized, double-blind, placebo-controlled trial compared the safety and efficacy of intravenous KYTRIL (3 mg) plus 8 mg dexamethasone phosphate with that of i.v. KYTRIL alone (3 mg) in the prevention of emesis induced by cytotoxic chemotherapy.

A total of 278 patients received one of the following agents as their main cytotoxic therapy, either as a single agent or in combination with other cytotoxic agents: carboplatin > 300 mg/m^2, cisplatin > 20 mg/m^2 to < 50 mg/m^2, dacarbazine > 350 mg/m^2 to < 500 mg/m^2, cyclophosphamide > 500 mg/m^2 in combination, doxorubicin > 40 mg/m^2 as single agent, doxorubicin >25 mg/m^2 in combination, epirubicin > 75 mg/m^2 as single agent, epirubicin >50 mg/m^2 in combination.

Patients received chemotherapy on Day 0 and were followed up to a further 6 days.

For the efficacy parameter of total control, there was a significantly better response in the group of patients treated with KYTRIL/dexamethasone than in the group of patients treated with KYTRIL/placebo on Day 0 (p=0.020) [95% CI (2.2%, 24.2%)] (see Table 9).

Table 9. Summary of Total Control[1] on Day 0 (Number (%) of Patients)

	Treatment Group		
	KYTRIL/Dexamethasone (n=141)	KYTRIL/Placebo (n=137)	P-value
Day 0	103 (73.0%)	82 (59.9%)	0.020

[1] Patients with no vomiting, no nausea, no rescue therapy and not withdrawn.

In addition, a statistically significant difference between the treatment groups was observed over the seven day period for the parameters of time to first rescue medication, time to first vomiting episode and time to first moderate/severe nausea.

Oral:
Oral KYTRIL prevents nausea and vomiting associated with emetogenic cancer therapy as shown by 24-hour efficacy data from three double-blind studies. The first trial compared oral doses of KYTRIL of 0.25 mg to 2.0 mg b.i.d. in 930 cancer patients receiving, principally, cyclophosphamide, carboplatin, or cisplatin (20 mg/m^2 to 50 mg/m^2) as chemotherapeutic agents. Table 10 summarizes the results of this study. The 1.0 mg b.i.d. dose of oral KYTRIL was demonstrated to produce the highest therapeutic benefit.

Table 10. Prevention of Nausea and Vomiting 24 Hours Post-Chemotherapy[1] Percentages of Patients

Efficacy Measures	Oral Dose of KYTRIL			
	0.25 mg b.i.d. (n=229) %	0.5 mg b.i.d. (n=235) %	1.0 mg b.i.d. (n=233) %	2.0 mg b.i.d. (n=233) %
Complete Response[2]	61	70*	81*+	72*
No Vomiting	66	77*	88*	79*
No Nausea	48	57	63*	54

1 Chemotherapy included oral and injectable cyclophosphamide, carboplatin, cisplatin (20 mg/m^2 to 50 mg/m^2), dacarbazine, doxorubicin, epirubicin.

2 No vomiting, no moderate or severe nausea, no rescue medication, and not withdrawn/discontinued during treatment period.

* Statistically significant ($p<0.01$) vs. 0.25 mg b.i.d.

\+ Statistically significant ($p<0.01$) vs. 0.5 mg b.i.d.

A second double-blind randomized trial compared oral KYTRIL 1.0 mg, b.i.d., oral KYTRIL plus dexamethasone, and metoclopramide plus dexamethasone in 357 patients receiving cisplatin (mean dose > 80 mg/m^2). The complete response rate for the regimen with KYTRIL plus dexamethasone was significantly better than for KYTRIL alone, or the regimen with metoclopramide plus dexamethasone. Table 11 summarizes the results of this study.

Table 11. Prevention of Nausea and Vomiting 24 Hours Post-High Dose Cisplatin Therapy (Percentage of Patients)

Efficacy Measures	Antiemetic Regimen		
	oral KYTRIL 1.0 mg b.i.d. (n=119) %	oral KYTRIL 1.0 mg b.i.d. plus Dexamethasone 12 mg IV (n=117) %	Metoclopramide 7 mg/kg IV plus Dexamethasone 12 mg IV (n=121) %
Complete Response[1]	52	65*	52
No Vomiting	56	66	52
No Nausea	45	57	39

[1] No emetic episodes, no moderate or severe nausea, no rescue medication, and not withdrawn/discontinued during treatment period.

* Statistically significant ($p<0.05$) vs. oral KYTRIL alone and vs. metoclopramide plus dexamethasone.

The third study compared once daily versus twice daily dosing regimes with 2 mg/day of oral granisetron in 700 patients. Approximately 50% of patients who received granisetron 2 mg daily administered either as a single dose (n = 344) or in divided doses (n = 356), were free of emetic episodes and nausea and did not require antiemetic rescue treatment during the 24-hour post-chemotherapy period.

The continued efficacy of granisetron tablets 2 mg u.i.d. or 1 mg b.i.d., administered on the day of chemotherapy only, has not been investigated beyond the 24 hour post-chemotherapy period. It is not known whether additional doses confer efficacy beyond 24 hours.

No controlled study has been performed to compare the antiemetic efficacy of granisetron tablets and granisetron injection at the recommended therapeutic doses.

Radiation-Induced Nausea and Vomiting:

Oral:
Oral KYTRIL prevents nausea and vomiting associated with total body irradiation and fractionated abdominal radiation.

Total Body Irradiation:
In a double-blind randomized study, 18 patients receiving KYTRIL Tablets, 2 mg daily, experienced significantly greater antiemetic protection for patients receiving total body irradiation compared to patients in a historical negative control group who received conventional (non-5-HT_3 antagonist) antiemetics. Total body irradiation consisted of 11 fractions of 120 cGy administered over 4 days, with 3 fractions on each of the first 3 days, and two fractions on the fourth day. Eight of the 18 patients received the full 11 fractions of total body irradiation. KYTRIL Tablets were given one hour before the first irradiation fraction of each day.

Twenty-two percent (22%) of patients treated with KYTRIL Tablets for the entire 4 day dosing period did not experience vomiting or receive antiemetics, compared to 0% of patients in the historical negative control group (n=90) ($p<0.01$). Patients who received KYTRIL Tablets also experienced significantly fewer emetic episodes during the first day of radiation and over the 4-day treatment period, compared to patients in the historical negative control group. The median time to the first emetic episode was 36 hours for patients who received KYTRIL Tablets.

Fractionated Abdominal Radiation:
The efficacy of KYTRIL, 2 mg daily, was evaluated in a double-blind, placebo-controlled randomized trial of 260 patients. KYTRIL Tablets were given 1 hour before radiation, composed of up to 20 daily fractions of 180 to 300 cGy each. The exceptions were patients with seminoma or those receiving whole abdomen irradiation who initially received 150 cGy per fraction. Radiation was administered to the upper abdomen with a field size of at least 100 cm^2.

Patients treated with KYTRIL Tablets (n=134) had a significantly longer time to the first episode of vomiting (35 vs. 9 days, p<0.001) relative to those patients who received placebo (n=126). Overall, 58% of the patients who received KYTRIL did not vomit compared to 42% of patients who received placebo (p=0.0047).

Patients treated with KYTRIL Tablets also had a significantly longer time to the first episode of nausea (11 vs. 1 day, p<0.001), relative to the placebo treated patients. Overall, 31% of the patients who received KYTRIL Tablets and 17% of patients who received placebo were nausea-free (p=0.0042).

Prevention of Postoperative Nausea and Vomiting:

Injection:

The efficacy of KYTRIL for prevention of postoperative nausea and vomiting was evaluated in 868 patients, of which 833 were women, 35 men, 484 Caucasians, 348 Asians, 18 Blacks, 18 Other, with 61 patients 65 years or older. KYTRIL was evaluated in two randomized, double-blind, placebo-controlled studies in patients who underwent elective gynecological surgery or cholecystectomy and received general anesthesia. Patients received a single intravenous dose of KYTRIL (0.1 mg, 1 mg or 3 mg) or placebo either 5 minutes before induction of anesthesia or immediately before reversal of anesthesia. The primary endpoint was the proportion of patients with no vomiting for 24 hours after surgery. Episodes of nausea and vomiting and use of rescue antiemetic therapy were recorded for 24 hours after surgery. In both studies, KYTRIL Injection (1 mg) was more effective than placebo in preventing postoperative nausea and vomiting (see Table 12). No additional benefit was seen in patients who received the 3 mg dose.

Table 12. Prevention of Postoperative Nausea and Vomiting in Adult Patients

Study and Efficacy Endpoint	Placebo	KYTRIL 0.1 mg	KYTRIL 1 mg	KYTRIL 3 mg
Study 1				
Number of Patients	**133**	**132**	**134**	**128**
No Vomiting				
0 to 24 hours	34%	45%	63%**	62%**
No Nausea				
0 to 24 hours	22%	28%	50%**	42%**
No Nausea or Vomiting				
0 to 24 hours	18%	27%	49%**	42%**
No Use of Rescue Antiemetic Therapy				
0 to 24 hours	60%	67%	75%*	77%*
Study 2				
Number of Patients	**117**	**–**	**110**	**114**
No Vomiting				
0 to 24 hours	56%	–	77%**	75%*
No Nausea				
0 to 24 hours	37%	–	59%**	56%*

*P<0.05

**P<0.001 versus placebo

Note: No Vomiting = no vomiting and no use of rescue antiemetic therapy; No Nausea = no nausea and no use of rescue antiemetic therapy

Gender/Race

There were too few male and Black patients to adequately assess differences in effect in either population.

Treatment of Postoperative Nausea and Vomiting:

Injection

The efficacy of KYTRIL for treatment of postoperative nausea and vomiting was evaluated in 844 patients, of which 731 were women, 113 men, 777 Caucasians, 6 Asians, 41 Blacks, 20 Other, with 107 patients 65 years or older. KYTRIL was evaluated in two randomized, double-blind, placebo-controlled studies of adult surgical patients who received general anesthesia with no prophylactic antiemetic agent, and who experienced nausea or vomiting within 4 hours postoperatively. Patients received a single intravenous dose of KYTRIL (0.1 mg, 1 mg or 3 mg) or placebo after experiencing postoperative nausea or vomiting. Episodes of nausea and vomiting and use of rescue antiemetic therapy were recorded for 24 hours after administration of study medication. KYTRIL was more effective than placebo in treating postoperative nausea and vomiting (see Table 13). No additional benefit was seen in patients who received the 3 mg dose.

Table 13. Treatment of Postoperative Nausea and Vomiting in Adult Patients

Study and Efficacy Endpoint	Placebo	KYTRIL 0.1 mg	KYTRIL 1 mg	KYTRIL 3 mg
Study 3				
Number of Patients	133	128	133	125
No Vomiting				
0 to 6 hours	26%	53%***	58%***	60%***
0 to 24 hours	20%	38%***	46%***	49%***
No Nausea				
0 to 6 hours	17%	40%***	41%***	42%***
0 to 24 hours	13%	27%**	30%**	37%***
No Use of Rescue Antiemetic Therapy				
0 to 6 hours	–	–	–	–
0 to 24 hours	33%	51%**	61%***	61%***
Study 4				
Number of Patients (All Patients)	162	163	–	–
No Vomiting				
0 to 6 hours	20%	32%*	–	–
0 to 24 hours	14%	23%*	–	–
No Nausea				
0 to 6 hours	13%	18%	–	–
0 to 24 hours	9%	14%	–	–
No Nausea or Vomiting				
0 to 6 hours	13%	18%	–	–
0 to 24 hours	9%	14%	–	–
No Use of Rescue Antiemetic				

Study and Efficacy Endpoint	Placebo	KYTRIL 0.1 mg	KYTRIL 1 mg	KYTRIL 3 mg
Therapy				
0 to 6 hours	–	–	–	–
0 to 24 hours	24%	34%*	–	–
Number of Patients (Treated for Vomiting)[1]	86	103	–	–
No Vomiting				
0 to 6 hours	21%	27%	–	–
0 to 24 hours	14%	20%	–	–

*P<0.05
**P<0.01
***P<0.001 versus placebo
[1] Protocol Specified Analysis: Patients who had vomiting prior to treatment
Note: No vomiting = no vomiting and no use of rescue antiemetic therapy; No nausea = no nausea and no use of rescue antiemetic therapy.

Gender/Race
There were too few male and Black patients to adequately assess differences in effect in either population.

DETAILED PHARMACOLOGY

Radioligand binding studies have been performed on rat and guinea pig brain membrane preparations. Granisetron appears to possess a high specificity for the 5-HT_3 receptor, while exhibiting negligible affinity for other 5-HT receptor subtypes (5-HT_1, 5-HT_2, 5-HT_{1A}, 5-$HT_{1B/C}$, 5-HT_{1C}) or $\propto_1$, $\propto_2$, or β-adrenoreceptors; dopamine-D_2, histamine-H_1, benzodiazepine, picrotoxin, or opioid binding sites.

The antagonistic effects of granisetron have been demonstrated in three models of 5-HT_3 receptor dependent activities. 1) transient bradycardia (the Von Bezold-Jarisch reflex) following the intravenous injection of 5-HT into anesthetized rats (IC_{50} = 0.7 mcg/kg), 2) 5-HT-induced contractions of the guinea pig isolated ileum (pA_2 = 8.1), and 3) tachycardia following 5-HT injection into the carotid arteries of the rabbit isolated heart (pA_2 = 10.7)

Two metabolites of granisetron (7-hydroxy metabolite and desmethyl metabolite) antagonized the Von Bezold-Jarisch reflex in anesthetized rats with potencies similar to that for the parent compound. However, the low plasma concentrations of these metabolites relative to the parent compound suggest that they are not likely to play a significant role following administration of granisetron.

Granisetron has proved efficacious both for the prophylaxis and treatment of emesis induced in the ferret by cisplatin, doxorubicin + cyclophosphamide, or X-irradiation. Maximal antiemetic efficacy in ferrets appeared to be achieved at a dose of 0.5 mg/kg i.v. administered 15 min. before chemotherapy or radiation therapy. Furthermore, when a 0.5 mg/kg i.v. dose of granisetron was administered during emetic episodes occurring 90 min. after cisplatin treatment, cessation of emesis was observed within 5 to 30 sec. of injection.

Granisetron was however, ineffective as an antiemetic in a canine model of apomorphine-evoked emesis and a ferret model of morphine-induced emesis suggesting that dopamine D_2 and opioid receptor antagonism are not components of its mechanism of action.

Other than for some inhibition of locomotor activity in mice at 10 mcg/kg s.c. and in rats at 1 to 5 mg/kg s.c., granisetron did not exert central nervous system effects in the models studied. At cumulative doses up to 4.3 mg/kg i.v. administered over 2 hrs, granisetron had no effect on basal blood pressure or heart rate in conscious male rats. In the anaesthetized dog, however, granisetron was demonstrated to decrease arterial blood pressure, heart rate, and myocardial contractility in a dose-dependent manner over a 1 to 3 mg/kg dose range.

Gastrointestinal: Granisetron (0.1 - 1.0 mg/kg s.c.) was associated with reduced faecal pellet output in conscious mice, suggesting a constipating effect.

Reproductive: Granisetron inhibited 5-HT induced contractions of the non-pregnant rat uterus *in vitro* with an IC_{50} of 5.9 mcM.

Preclinical Pharmacokinetics:
Pharmacokinetics and ADME of granisetron have been extensively studied in rat and dog, the main species used in the non-clinical toxicology studies. Information has also been obtained on the mouse (used for carcinogenicity assessment), rabbit (teratology assessment) and ferret (efficacy pharmacology).

In rat and dog after intravenous dosing, granisetron freely diffused between plasma and red cells. Plasma protein binding in rats and dogs was moderate, 57% and 45%, respectively. A volume of distribution equivalent to approximately 3 L/kg in both species reflected the extensive tissue uptake expected of a lipophilic amine. In the rat, low excretion of granisetron in urine (approximately 2% dose) and a total plasma clearance (3.7 L/h/kg) similar to hepatic blood flow classified granisetron as a highly extracted drug whose clearance was flow-rate limited. In the dog, the plasma clearance value (2.6 L/h/kg) and the low urinary excretion (2-4% dose) classified granisetron extraction as medium to high in this species. In both species, relatively short granisetron plasma half-lives were observed (approximately 0.7 hours) and linear kinetics were indicated by the proportionate increases of granisetron plasma AUC with dose. As expected, no accumulation was observed on repeated daily dosing.

Complete absorption of ^{14}C-granisetron from the gastrointestinal tract in rats, dogs, mice and rabbits was observed. However, oral bioavailability was severely reduced by the large first-pass effect resulting from the high liver extraction. Thus in rats, granisetron bioavailability was estimated at 0.2% of the dose after an oral dose of 5 mg/kg, whilst in dogs oral bioavailability was higher (about 17% at 0.25 and 1.5 mg/kg p.o.) reflecting lower liver extraction. In both species, bioavailability increased at the high dose levels used in the toxicology studies (rat: about 10% bioavailability at 100 mg/kg p.o.; dogs: about 80% at 10 mg/kg p.o.), as the increased drug input partially saturated the first-pass effect.

Granisetron-related material (radioactivity) was rapidly and widely distributed to tissues after intravenous or oral doses of ^{14}C -granisetron to rats. Whole body autoradiography and direct measurement revealed relatively high concentrations in excretory organs, liver and kidney, and low concentrations in blood and brain tissue. The time-course of elimination from tissues was similar to that from blood. The radioactivity was readily eliminated, such that only 1% remained in the tissues at 24 hours, though trace amounts were eliminated more slowly. Like many amine drugs, small amounts were taken up by melanin-containing tissues in pigmented animals and slowly released. On daily repeated intravenous dosing, minimal accumulation of radioactivity was observed in blood and tissues.

Granisetron was extensively metabolised, resulting in low excretion of unchanged drug in urine and feces. Metabolites found in mice, rats, rabbits, dogs and ferrets revealed that similar metabolic processes (oxidation at the N-methyl groups, oxidation in the benzenoid ring followed by sulphate and glucuronide conjugation, and a combination of these) were used in all species. However, quantitative differences between species were observed. Notably, 5-hydroxylation was higher than 7-hydroxylation in rats, mice and rabbits, whilst the converse was true for dogs and ferrets. Excretion of granisetron itself was low (no more than 13%) in all species studied. Granisetron excretion in feces accounted for less than 3% of the dose. Granisetron metabolites were readily excreted in both urine and feces of mice, rats, rabbits, dogs and ferrets. On administering ^{14}C -granisetron, urinary excretion of radioactivity in rats and dogs amounted to approximately 40% of the dose, irrespective of dose route, and the remainder was excreted in feces. In mice and rabbits, the urinary route accounted for about 60% dose, and in ferrets about 20% dose. The majority of urinary excretion occurred in the first 24 hours after dosing.

TOXICOLOGY

Acute Toxicity:

The acute toxicity of granisetron is due primarily to CNS stimulation. LD_{50} values by the intravenous route are within the range of 14 to 25 mg/kg in rats and mice.

The intravenous LD_{50} for granisetron hydrochloride in mice is 17 mg/kg in males and 25 mg/kg in females. In rats it is 14 mg/kg in males and 16 mg/kg in females. The oral LD_{50} is 350 mg/kg in both male and female mice. It is 350 mg/kg in male rats and 1100 mg/kg in female rats.

Longterm Toxicity:

Subacute Toxicity Studies

The subacute toxicity of granisetron was studied in the rat and dog; both species are suitable for the safety evaluation of KYTRIL (granisetron hydrochloride) on pharmacokinetic and metabolic grounds. In intravenous studies of up to 3 months duration in the rat, signs of acute CNS stimulation were dose limiting at 9 mg/kg/day. Histopathological examination revealed an increase in the fat content of the liver in the majority of females at 6 mg/kg/day after 13 weeks of treatment but not following a further 4 weeks off-dose. In the dog, intravenous studies of up to 3 months duration resulted in convulsions at near lethal doses (3 mg/kg/day). Increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were seen in some animals at 3 mg/kg/day but there were no histopathological findings to indicate target organ

toxicity at this level. Following treatment for 3 months, the intravenous no-toxic-effect level in both species was 0.5 mg/kg/day, representing a factor of approximately 3 over the maximum anticipated daily clinical dose of KYTRIL**.**

Chronic Toxicity Studies

Granisetron was administered in oral repeat-dose studies of up to 12 months duration in the rat and dog.

In the 6 and 12 month rat studies, there were changes in plasma enzymes associated with liver function, however, none of these changes was evident in sub-groups of high dose animals maintained for an off-dose period after the treatment. Dose-related increases in liver weights were also seen in rats given granisetron for up to 52 weeks, in the diet; such increases occurred in males dosed at 25 mg/kg/day and above.

Morphometric analysis has confirmed that there was an increased number of hepatocytes per unit area at the high dose, indicating that the increased liver weights were associated with hepatocyte hyperplasia. There was no evidence of hyperplasia at a dose of 5 mg/kg/day. Although there were increased incidences of rats with foci or areas of acidophilic and/or basophilic hepatocyte alteration in the intermediate and high dose groups, precise morphometric quantification of the amount of liver occupied by foci demonstrated that increases compared with the controls were confined to the high dose. These results clearly define 5 mg/kg/day to be a no-effect dose, at which the drug does not cause the production of liver foci or induce hyperplasia. The morphometric analysis also showed that, at the high dose, the amount of liver occupied by foci regressed after cessation of treatment.

In the 6 month dog study, there was a trend toward increased alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) at the high dose of 10 mg/kg/day, although histopathological changes were not observed. Physical signs at the high dose during the initial stages of treatment consisted of prominence of the nictating membrane, black or dark discoloured feces and, in males, an increased incidence of loose feces. Emesis and isolated clonic convulsions were also noted. One high dose male died on Day 181 having shown no previous signs of ill health; the cause of death could not be established. There were no toxic effects at the mid-dose of 1.5 mg/kg/day.

In the 12 month dog study, the high dose (5 mg/kg/day) produced no CNS effects and there were no changes in plasma enzymes indicative of altered hepatic function or treatment related histopathological findings at this dose.

Carcinogenicity Studies

In a 24-month carcinogenicity study, mice were treated orally with granisetron 1, 5 or 50 mg/kg/day. There was a statistically significant increase in the incidence of hepatocellular carcinomas in males and hepatocellular adenomas in females dosed with 50 mg/kg/day (5,000 times the recommended human dose given intravenously). No increase in liver tumours was observed in mice at a dose of 5 mg/kg/day (500 times the recommended human dose given intravenously).

In a 24-month carcinogenicity study, rats were treated orally with granisetron 1, 5 or 50 mg/kg/day. Owing to manifestations of toxicity, the 50 mg/kg dose was reduced to 25 mg/kg/day (2,500 times the recommended human dose given intravenously) from week 59 of treatment onwards. There was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in males dosed with 5 mg/kg/day (500 times the recommended human dose given intravenously) and above, and in females dosed with 50 mg/kg/day (5,000 times the recommended human dose given intravenously). No increase in liver tumors was observed in rats at a dose of 1 mg/kg/day (100 times the recommended human dose, given intravenously) in males and 5 mg/kg/day (500 times the recommended human dose given intravenously) in females.

Experimental evidence in rats shows that granisetron exhibits the characteristics of a promoter of liver tumors with a clear no-effect dose of 1 mg/kg (100 times the recommended human dose given intravenously). 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 (10,000 times the recommended human dose given intravenously), the observed promoting effects were reversible upon cessation of treatment. Additionally, there was no adverse effect on the liver of dogs treated for 12 months with granisetron, 5 mg/kg/day (500 times the recommended human dose given intravenously).

Mutagenicity Studies

The effects of granisetron were investigated in a battery of seven tests for mutagenicity, including an investigation of DNA damage in rat hepatocytes. Granisetron did not cause gene mutation in Ames 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 at doses of up to 1800 times the recommended human dose given intravenously. However, granisetron was associated with a significant increase in the number of cells with polyploidy in an *in vitro* human lymphocyte chromosomal aberration test. There was no evidence of DNA damage and repair in assays of unscheduled DNA synthesis (UDS) in rat hepatocytes *in vitro* (or *in vivo* at doses of up to 35,000 times the recommended human dose given intravenously). 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 methodology and microscopic examination of HeLa cells, 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.

Reproduction

In a reproduction and fertility study in rats, granisetron at subcutaneous doses up to 6 mg/kg/day (600 times the recommended human dose given intravenously) had no effect on male or female fertility.

At dose levels which produced maternal toxicity, intravenous granisetron [up to 9 mg/kg/day (900 times the recommended human dose given intravenously) in rats, and up to 3 mg/kg/day (300 times the recommended human dose given intravenously) in rabbits] had no adverse effect

on the course and outcome of pregnancy. A similar lack of effect was apparent in peri- and post-natal studies and general reproductive studies, in the rat.

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PART III: CONSUMER INFORMATION

PrKYTRIL®
Granisetron hydrochloride tablets
Granisetron hydrochloride injection

This leaflet is part III of a three-part "Product Monograph" published when KYTRIL was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about KYTRIL. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
KYTRIL is one of a group called antiemetics and it can only be obtained with a prescription from your doctor.

KYTRIL is intended to prevent nausea (feeling sick) and vomiting which may occur after you receive cancer chemotherapy or radiotherapy, or after surgery.

What it does:
Cancer chemotherapies, radiation therapies, and surgery are thought to cause the release of serotonin, a natural substance in the body. Serotonin can cause you to feel sick and to vomit. Granisetron, the active ingredient in KYTRIL tablets, will stop the action of serotonin and help prevent you from feeling sick and vomiting.

When it should not be used:
Do not take this medicine if you are allergic to granisetron or any of the ingredients KYTRIL contains.

What the medicinal ingredient is:
Granisetron hydrochloride

What the nonmedicinal ingredients are:
Each tablet contains the following inactive ingredients: hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, sodium starch glycollate and Opadry® YS-1-18027-A (hypromellose, titanium dioxide, macrogol 400, and polysorbate 80).

Each injection contains the following inactive ingredients: sodium chloride, benzyl alcohol, citric acid monohydrate, water for injection and hydrochloric acid and/or sodium hydroxide for pH adjustment.

What dosage forms it comes in:
KYTRIL tablets are supplied in two strengths: 1 mg and 2 mg tablets.

KYTRIL injections are supplied in clear glass multi-use vials of 1 mL or 4 mL packaged in boxes of 1 vial. Each vial contains 1 mg/mL granisetron as hydrochloride.

WARNINGS AND PRECAUTIONS

BEFORE you use KYTRIL talk to your doctor or pharmacist if:

- you have any allergies to similar antiemetics such as dolasetron mesylate (Anzemet®) or ondansetron (Zofran®)
- you are pregnant, plan to become pregnant or are breastfeeding
- you have liver problems
- you have a history of heart problems
- you have been told by a doctor that you have a blockage of your gut or if you have severe constipation, pain or swelling in your stomach
- you are taking other medications, including drugs you can buy without a prescription and herbal products.

As KYTRIL may cause drowsiness, you should avoid driving a car or operating hazardous machinery until you know it does not affect you.

PROPER USE OF THIS MEDICATION

This medicine is only for you, the person for whom the prescription was written. Do not give this medication to others.

Usual adult dose:
Follow your doctor's instructions about how often you should take your medicine and how many tablets you should take. This information is also on the label of the container of your medicine and if not, of if you have any questions, you should consult your doctor or pharmacist.

Kytril injection will be given to you by hospital staff before and/or after your therapy or surgery.

Do not take more tablets or take your tablets more often than your doctor prescribes.

Overdose:
In the event that you accidentally take more tablets than your doctor prescribes, immediately contact your doctor, hospital emergency department, or the nearest poison control centre, even if you do not feel ill.

Missed Dose:
If you forget to take a tablet at the time it should be taken, take the tablet as soon as you remember it was missed.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

If you experience an allergic reaction (e.g. shortness of breath,

drop in blood pressure, skin lumps or hives), contact your doctor immediately. Do not take any more medicine unless instructed to do so by your doctor.

If you experience symptoms of heart problems such as palpitations (fast, pounding or irregular heart beat), chest pain, dizziness or fainting, tell your doctor or nurse immediately.

You may experience headaches, constipation, weakness, sleepiness, diarrhea or abdominal pain while taking KYTRIL. You may also experience pain, anemia or fever while on KYTRIL injection therapy. There is no need to stop the medicine but you should tell your doctor about these symptoms.

This is not a complete list of side effects. For any unexpected effects while taking KYTRIL, contact your doctor or pharmacist.

HOW TO STORE IT

KYTRIL tablets should be kept at controlled room temperature (15° - 30°C) in their original pack.

KYTRIL IV should be stored at controlled room temperature (15° - 30°C). Discard unused portion. Protect form light. The vial should be used within 30 days once opened.

The expiry date of this medicine is printed on the label. Do not use the medicine after this date. Keep your medicine in a safe place out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345
By toll-free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.rochecanada.com or by contacting the sponsor, Hoffmann-La Roche Ltd, at: 1-888-762-4388.

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