

KYTRIL® (granisetron hydrochloride) Injection, Tablets and Oral Solution

Before prescribing, please see complete product information, a summary of which follows:

INDICATIONS AND USAGE: KYTRIL Injection is indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin, and the prevention and treatment of postoperative nausea and vomiting. KYTRIL Tablets and Oral Solution are also indicated for the prevention of nausea and vomiting associated with radiation, including total body irradiation and fractionated abdominal radiation.

CONTRAINDICATIONS: In patients with known hypersensitivity to the drug or any of its components.

WARNINGS: Hypersensitivity reactions may occur in patients who have exhibited hypersensitivity to other selective 5-HT₃ receptor antagonists.

PRECAUTIONS: 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.

Drug Interactions: Granisetron does not induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system. There have been no definitive drug-drug interaction studies to examine pharmacokinetic or pharmacodynamic interaction with other drugs but, in humans, KYTRIL Injection has been safely administered with drugs representing benzodiazepines, neuroleptics, and anti-ulcer medications commonly prescribed with antiemetic treatments. KYTRIL Injection also does not appear to interact with emetogenic cancer chemotherapies. Because granisetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes, inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of granisetron.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 24-month carcinogenicity study, rats were treated orally with granisetron 1, 5 or 50 mg/kg/day (6, 30 or 300 mg/m²/day). The 50 mg/kg/day dose was reduced to 25 mg/kg/day (150 mg/m²/day) during week 59 due to toxicity. For a 50 kg person of average height (1.46 m² body surface area), these doses represent 16, 81, and 405 times the recommended IV clinical dose (0.37 mg/m², IV) or 4, 20 and 101 times the recommended oral clinical dose (1.48 mg/m²) on a body surface area basis. There was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in males treated with 5 mg/kg/day (30 mg/m²/day, 81 times the recommended IV human dose and 20 times the recommended oral human dose based on body surface area) and above, and in females treated with 25 mg/kg/day (150 mg/m²/day, 405 times the recommended IV human dose and 101 times the recommended oral human dose based on body surface area). No increase in liver tumors was observed at a dose of 1 mg/kg/day (6 mg/m²/day, 16 times the recommended IV human dose and 4 times the recommended oral human dose based on body surface area) in males and 5 mg/kg/day (30 mg/m²/day, 81 times the recommended IV human dose and 20 times the recommended oral human dose based on body surface area) in females. In a 12-month oral toxicity study, treatment with granisetron 100 mg/kg/day (600 mg/m²/day, 1622 times the recommended IV human dose and 405 times the recommended oral human dose based on body surface area) produced hepatocellular adenomas in male and female rats while no such tumors were found in the control rats. A 24-month mouse carcinogenicity study of granisetron did not show a statistically significant increase in tumor incidence, but the study was not conclusive.

Because of the tumor findings in rat studies, prescribe KYTRIL only at the dose and for the indication recommended (see INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION). Granisetron was not mutagenic in *in vitro* Ames test and mouse lymphoma cell forward mutation assay, and *in vivo* mouse micronucleus test and *in vitro* and *ex vivo* rat hepatocyte UDS assays. It, however, produced a significant increase in UDS in HeLa cells *in vitro* and a significant increased incidence of cells with polyploidy in an *in vitro* human lymphocyte chromosomal aberration test. Granisetron at subcutaneous doses up to 6 mg/kg/day (36 mg/m²/day, 97 times the recommended human dose based on body surface area) or at oral doses up to 100 mg/kg/day (600 mg/m²/day, 405 times the recommended human oral dose based on body surface area) had no effect on fertility and reproductive performance of male and female rats.

Pregnancy Category B. Reproduction studies performed in pregnant rats at IV doses up to 9 mg/kg/day (54 mg/m²/day, 146 times the recommended human IV dose based on body surface area) and pregnant rabbits at IV doses up to 3 mg/kg/day (35.4 mg/m²/day, 96 times the recommended human IV dose based on body surface area) revealed no evidence of impaired fertility or harm to the fetus due to granisetron. Reproduction studies performed in pregnant rats at oral doses up to 125 mg/kg/day (750 mg/m²/day, 507 times the recommended human oral dose based on body surface area) and pregnant rabbits at oral doses up to 32 mg/kg/day (378 mg/m²/day, 255 times the recommended human oral dose based on body surface area) revealed no evidence of impaired fertility or harm to the fetus due to granisetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use KYTRIL during pregnancy only if clearly needed.

Nursing mothers: It is not known whether granisetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when KYTRIL is administered to a nursing woman.

Pediatric oral: Safety and effectiveness in pediatric patients have not been established.

Pediatric injection: See DOSAGE AND ADMINISTRATION (see complete Product Information) for use in chemotherapy-induced nausea and vomiting in pediatric patients 2-16 years of age. Safety and effectiveness in pediatric patients under 2 years of age have not been established. Safety and effectiveness of KYTRIL Injection have not been established in pediatric patients for the prevention or treatment of postoperative nausea or vomiting.

Geriatric oral: Efficacy and safety were maintained with increasing age.

Geriatric injection: Effectiveness and safety were similar in patients of various ages.

ADVERSE REACTIONS: Postoperative Nausea and Vomiting. The adverse events listed in Table 1 were reported in ≥2% of adults receiving KYTRIL Injection 1 mg during controlled clinical trials.

Table 1. 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	6.0	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

(Continued)

KYTRIL® (granisetron hydrochloride) Injection, Tablets and Oral Solution

Table 1. Adverse Events ≥2% (Continued)

	Percent of Patients With Event	
	KYTRIL Injection 1 mg (n=267)	Placebo (n=266)
Flatulence	3.0	3.0
Infection	3.0	2.3
Dyspepsia	3.0	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 above in Table 1. 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%).

Chemotherapy-Induced Nausea and Vomiting. The following are the comparative frequencies of the five most commonly reported adverse events (≥3%) in patients receiving IV KYTRIL, 40 mcg/kg, in single-day chemotherapy, controlled clinical trials. Patients received chemotherapy, primarily cisplatin, and intravenous fluids during the 24-hour period following KYTRIL Injection administration. 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. The following principal adverse effects were seen in single-day chemotherapy clinical trials evaluating KYTRIL Injection (40 mcg/kg) vs. comparators (metoclopramide/dexamethasone and phenothiazines/dexamethasone): headache (14% vs. 6%); asthenia (5% vs. 6%); somnolence (4% vs. 15%); diarrhea (4% vs. 6%) and constipation (3% vs. 3%), respectively. Adverse events were generally recorded over 7 days post-KYTRIL Injection administration.

In over 3000 patients receiving KYTRIL Injection (2 to 160 mcg/kg) in single-day and multiple-day clinical trials with emetogenic cancer therapies, adverse events, other than those above, were observed; attribution of many of these events to KYTRIL is uncertain.

In comparative trials, mainly with cisplatin regimens, elevations of AST and ALT (>2 times the upper limit of normal) following administration of KYTRIL Injection occurred in 2.8% and 3.3% of patients, respectively. These frequencies were not significantly different from those seen with comparators (AST: 2.1%; ALT: 2.4%). Hypertension (2%); hypotension, arrhythmias such as sinus bradycardia, atrial fibrillation, varying degrees of A-V block, ventricular ectopy including non-sustained tachycardia, and ECG abnormalities have been observed rarely. Agitation, anxiety, CNS stimulation and insomnia were seen in less than 2% of patients. Extrapyramidal syndrome occurred rarely and only in the presence of other drugs associated with this syndrome; rare cases of hypersensitivity reactions, sometimes severe (eg, anaphylaxis, shortness of breath, hypotension, urticaria) have been reported; fever (3%); taste disorder (2%); skin rashes (1%). In multiple-day comparative studies, fever occurred more frequently with KYTRIL Injection (8.6%) than with comparative drugs (3.4%, $P < 0.014$), which usually included dexamethasone.

Over 3700 patients have received KYTRIL Tablets in clinical trials with emetogenic cancer therapies consisting primarily of cyclophosphamide or cisplatin regimens.

In patients receiving KYTRIL Tablets 1 mg bid for 1, 7 or 14 days, or 2 mg qd for 1 day, adverse experiences reported in more than 5% of the patients with comparator and placebo incidences are listed in Table 2.

Table 2. Principal Adverse Events in Clinical Trials

	Percent of Patients With Event			
	KYTRIL ¹ Tablets 1 mg bid (n=978)	KYTRIL ¹ Tablets 2 mg qd (n=1450)	Comparator ² (n=599)	Placebo (n=185)
Headache ³	21%	20%	13%	12%
Constipation	18%	14%	16%	8%
Asthenia	14%	18%	10%	4%
Diarrhea	8%	9%	10%	4%
Abdominal pain	6%	4%	6%	3%
Dyspepsia	4%	6%	5%	4%

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

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

³Usually mild to moderate in severity.

Other adverse events reported in clinical trials were: In single-day dosing studies in which adverse events were collected for 7 days, nausea (20%) and vomiting (12%) were recorded as adverse events after the 24-hour efficacy assessment period. In comparative trials, elevation of AST and ALT (>2 times the upper limit of normal) following the administration of KYTRIL Tablets occurred in 5% and 6% of patients, respectively. These frequencies were not significantly different from those seen with its comparator (AST: 2%; ALT: 9%). Hypertension (1%); hypotension, angina pectoris atrial fibrillation and syncope have been observed rarely. Dizziness (5%), insomnia (5%), anxiety (2%), somnolence (1%). One case compatible with but not diagnostic of extrapyramidal symptoms has been reported in a patient treated with KYTRIL Tablets. Rare cases of hypersensitivity reactions, sometimes severe (eg, anaphylaxis, shortness of breath, hypotension, urticaria) have been reported. Fever (5%). Events often associated with chemotherapy have also been reported: leukopenia (9%), decreased appetite (6%), anemia (4%), alopecia (3%), thrombocytopenia (2%).

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, asthenia, and constipation. Headache, however, was less prevalent in this patient population.

Rx only

Distributed by:



Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199
www.rocheusa.com

Revised 0802/0601