KYTRIL®

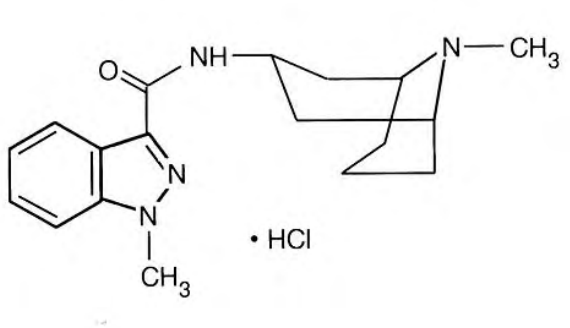
(granisetron hydrochloride)

INJECTION

Rx only

DESCRIPTION

KYTRIL (granisetron hydrochloride) Injection is an antinauseant and antiemetic agent. Chemically it is *endo*-N-(9-methyl-9-azabicyclo [3.3.1] non-3-yl)-1-methyl-1H-indazole-3-carboxamide hydrochloride with a molecular weight of 348.9 (312.4 free base). Its empirical formula is $C_{18}H_{24}N_4O$•HCl, while its chemical structure is:



granisetron hydrochloride

Granisetron hydrochloride is a white to off-white solid that is readily soluble in water and normal saline at 20°C. KYTRIL Injection is a clear, colorless, sterile, nonpyrogenic, aqueous solution for intravenous administration.

KYTRIL 1 mg/1 mL is available in 1 mL single-use and 4 mL multi-use vials. KYTRIL 0.1 mg/1 mL is available in a 1 mL single-use vial.

1 mg/1 mL: Each 1 mL contains 1.12 mg granisetron hydrochloride equivalent to granisetron, 1 mg; sodium chloride, 9 mg; citric acid, 2 mg; and benzyl alcohol, 10 mg, as a preservative. The solution's pH ranges from 4.0 to 6.0.

0.1 mg/1 mL: Each 1 mL contains 0.112 mg granisetron hydrochloride equivalent to granisetron, 0.1 mg; sodium chloride, 9 mg; citric acid, 2 mg. Contains no preservative. The solution's pH ranges from 4.0 to 6.0.

CLINICAL PHARMACOLOGY

Granisetron is a selective 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT$_1$; 5-HT$_{1A}$; 5-HT$_{1B/C}$; 5-HT$_2$; for alpha$_1$-, alpha$_2$- or beta-adrenoreceptors; for dopamine-D$_2$; or for histamine-H$_1$; benzodiazepine; picrotoxin or opioid receptors.

Serotonin receptors of the 5-HT_3 type are located peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. During chemotherapy-induced vomiting, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT_3 receptors. This evokes vagal afferent discharge and may induce vomiting. Animal studies demonstrate that, in binding to 5-HT_3 receptors, granisetron blocks serotonin stimulation and subsequent vomiting after emetogenic stimuli such as cisplatin. In the ferret animal model, a single granisetron injection prevented vomiting due to high-dose cisplatin or arrested vomiting within 5 to 30 seconds.

In most human studies, granisetron has had little effect on blood pressure, heart rate or ECG. No evidence of an effect on plasma prolactin or aldosterone concentrations has been found in other studies.

KYTRIL Injection exhibited no effect on oro-cecal transit time in normal volunteers given a single intravenous infusion of 50 mcg/kg or 200 mcg/kg. Single and multiple oral doses slowed colonic transit in normal volunteers.

Pharmacokinetics

Chemotherapy-Induced Nausea and Vomiting

In adult cancer patients undergoing chemotherapy and in volunteers, mean pharmacokinetic data obtained from an infusion of a single 40 mcg/kg dose of KYTRIL Injection are shown in **Table 1**.

Table 1 Pharmacokinetic Parameters in Adult Cancer Patients Undergoing Chemotherapy and in Volunteers, Following a Single Intravenous 40 mcg/kg Dose of KYTRIL Injection

	Peak Plasma Concentration (ng/mL)	Terminal Phase Plasma Half-Life (h)	Total Clearance (L/h/kg)	Volume of Distribution (L/kg)
Cancer Patients				
Mean	63.8*	8.95*	0.38*	3.07*
Range	18.0 to 176	0.90 to 31.1	0.14 to 1.54	0.85 to 10.4
Volunteers				
21 to 42 years				
Mean	64.3†	4.91†	0.79†	3.04†
Range	11.2 to 182	0.88 to 15.2	0.20 to 2.56	1.68 to 6.13
65 to 81 years				
Mean	57.0†	7.69†	0.44†	3.97†
Range	14.6 to 153	2.65 to 17.7	0.17 to 1.06	1.75 to 7.01

*5-minute infusion.
†3-minute infusion.

Distribution

Plasma protein binding is approximately 65% and granisetron distributes freely between plasma and red blood cells.

Metabolism

Granisetron metabolism involves N-demethylation and aromatic ring oxidation followed by conjugation. In vitro liver microsomal studies show that granisetron's major route of metabolism is inhibited by ketoconazole, suggestive of metabolism mediated by the cytochrome P-450 3A subfamily. Animal studies suggest that some of the metabolites may also have 5-HT_3 receptor antagonist activity.

Elimination

Clearance is predominantly by hepatic metabolism. In normal volunteers, approximately 12% of the administered dose is eliminated unchanged in the urine in 48 hours. The remainder of the dose is excreted as metabolites, 49% in the urine, and 34% in the feces.

Subpopulations

Gender

There was high inter- and intra-subject variability noted in these studies. No difference in mean AUC was found between males and females, although males had a higher C_{max} generally.

Elderly

The ranges of the pharmacokinetic parameters in elderly volunteers (mean age 71 years), given a single 40 mcg/kg intravenous dose of KYTRIL Injection, were generally similar to those in younger healthy volunteers; mean values were lower for clearance and longer for half-life in the elderly patients (see **Table 1**).

Pediatric Patients

A pharmacokinetic study in pediatric cancer patients (2 to 16 years of age), given a single 40 mcg/kg intravenous dose of KYTRIL Injection, showed that volume of distribution and total clearance increased with age. No relationship with age was observed for peak plasma concentration or terminal phase plasma half-life. When volume of distribution and total clearance are adjusted for body weight, the pharmacokinetics of granisetron are similar in pediatric and adult cancer patients.

Renal Failure Patients

Total clearance of granisetron was not affected in patients with severe renal failure who received a single 40 mcg/kg intravenous dose of KYTRIL Injection.

Hepatically Impaired Patients

A pharmacokinetic study in patients with hepatic impairment due to neoplastic liver involvement showed that total clearance was approximately halved compared to patients without hepatic impairment. Given the wide variability in pharmacokinetic parameters noted in patients, dosage adjustment in patients with hepatic functional impairment is not necessary.

Postoperative Nausea and Vomiting

In adult patients (age range, 18 to 64 years) recovering from elective surgery and receiving general balanced anesthesia, mean pharmacokinetic data obtained from a single

1 mg dose of KYTRIL Injection administered intravenously over 30 seconds are shown in **Table 2**.

Table 2 Pharmacokinetic Parameters in 16 Adult Surgical Patients Following a Single Intravenous 1 mg Dose of KYTRIL Injection

	Terminal Phase Plasma Half-Life (h)	Total Clearance (L/h/kg)	Volume of Distribution (L/kg)
Mean	8.63	0.28	2.42
Range	1.77 to 17.73	0.07 to 0.71	0.71 to 4.13

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

CLINICAL TRIALS

Chemotherapy-Induced Nausea and Vomiting

Single-Day Chemotherapy

Cisplatin-Based Chemotherapy

In a double-blind, placebo-controlled study in 28 cancer patients, KYTRIL Injection, 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 3**).

Table 3 Prevention of Chemotherapy-Induced Nausea and Vomiting — Single-Day Cisplatin Therapy[1]

	KYTRIL Injection	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 Injection infusion and continued for 1.5 to 3.0 hours. Mean cisplatin dose was 86 mg/m^2 in the KYTRIL Injection group and 80 mg/m^2 in the placebo group.

[2] No vomiting and no moderate or severe nausea.

KYTRIL Injection was also evaluated in a randomized dose response study of cancer patients receiving cisplatin ≥75 mg/m^2. Additional chemotherapeutic agents included: anthracyclines, carboplatin, cytostatic antibiotics, folic acid derivatives, methylhydrazine, nitrogen mustard analogs, podophyllotoxin derivatives, pyrimidine analogs, and vinca alkaloids. KYTRIL Injection doses of 10 and 40 mcg/kg were superior to 2 mcg/kg in preventing cisplatin-induced nausea and vomiting, but 40 mcg/kg was not significantly superior to 10 mcg/kg (see **Table 4**).

Table 4 Prevention of Chemotherapy-Induced Nausea and Vomiting — Single-Day High-Dose Cisplatin Therapy[1]

	KYTRIL Injection (mcg/kg)			P-Value (vs. 2 mcg/kg)	
	2	**10**	**40**	**10**	**40**
Number of Patients	52	52	53		
Response Over 24 Hours					
Complete Response[2]	31%	62%	68%	<0.002	<0.001
No Vomiting	38%	65%	74%	<0.001	<0.001
No More Than Mild Nausea	58%	75%	79%	NS	0.007

[1] Cisplatin administration began within 10 minutes of KYTRIL Injection infusion and continued for 2.6 hours (mean). Mean cisplatin doses were 96 to 99 mg/m^2.

[2] No vomiting and no moderate or severe nausea.

KYTRIL Injection was also 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 5**.

Table 5 Prevention of Chemotherapy-Induced Nausea and Vomiting — Single-Day High-Dose and Low-Dose Cisplatin Therapy[1]

	KYTRIL Injection (mcg/kg)				P-Value (vs. 5 mcg/kg)		
	5	**10**	**20**	**40**	**10**	**20**	**40**
High-Dose Cisplatin							
Number of Patients	40	49	48	47			
Response Over 24 Hours							
Complete Response[2]	18%	41%	40%	47%	0.018	0.025	0.004
No Vomiting	28%	47%	44%	53%	NS	NS	0.016
No Nausea	15%	35%	38%	43%	0.036	0.019	0.005
Low-Dose Cisplatin							
Number of Patients	42	41	40	46			
Response Over 24 Hours							
Complete Response[2]	29%	56%	58%	41%	0.012	0.009	NS
No Vomiting	36%	63%	65%	43%	0.012	0.008	NS
No Nausea	29%	56%	38%	33%	0.012	NS	NS

[1] Cisplatin administration began within 10 minutes of KYTRIL Injection infusion and continued for 2 hours (mean). Mean cisplatin doses were 64 and 98 mg/m^2 for low and high strata.

[2] No vomiting and no use of rescue antiemetic.

For both the low and high cisplatin strata, 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.

Moderately Emetogenic Chemotherapy

KYTRIL Injection, 40 mcg/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/m^2, cisplatin 20 to 50 mg/m^2 and cyclophosphamide >600 mg/m^2. KYTRIL Injection was superior to the chlorpromazine regimen in preventing nausea and vomiting (see **Table 6**).

Table 6 Prevention of Chemotherapy-Induced Nausea and Vomiting—Single-Day Moderately Emetogenic Chemotherapy

	KYTRIL Injection	Chlorpromazine[1]	P-Value
Number of Patients	133	133	
Response Over 24 Hours			
Complete Response[2]	68%	47%	<0.001
No Vomiting	73%	53%	<0.001
No More Than Mild Nausea	77%	59%	<0.001

[1] Patients also received dexamethasone, 12 mg.
[2] No vomiting and no moderate or severe nausea.

In other studies of moderately emetogenic chemotherapy, no significant difference in efficacy was found between KYTRIL doses of 40 mcg/kg and 160 mcg/kg.

Repeat-Cycle Chemotherapy

In an uncontrolled trial, 512 cancer patients received KYTRIL Injection, 40 mcg/kg, prophylactically, for two cycles of chemotherapy, 224 patients received it for at least four cycles, and 108 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 60% to 69%. No patients were studied for more than 15 cycles.

Pediatric Studies

A randomized double-blind study evaluated the 24-hour response of 80 pediatric cancer patients (age 2 to 16 years) to KYTRIL Injection 10, 20 or 40 mcg/kg. Patients were treated with cisplatin ≥60 mg/m^2, cytarabine ≥3 g/m^2, cyclophosphamide ≥1 g/m^2 or nitrogen mustard ≥6 mg/m^2 (see **Table 7**).

Table 7 Prevention of Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients

	KYTRIL Injection Dose (mcg/kg)		
	10	20	40
Number of Patients	29	26	25
Median Number of Vomiting Episodes	2	3	1
Complete Response Over 24 Hours[1]	21%	31%	32%

[1] No vomiting and no moderate or severe nausea.

A second pediatric study compared KYTRIL Injection 20 mcg/kg to chlorpromazine plus dexamethasone in 88 patients treated with ifosfamide ≥3 g/m^2/day for two or three days. KYTRIL Injection was administered on each day of ifosfamide treatment. At 24 hours, 22% of KYTRIL Injection patients achieved complete response (no vomiting and no moderate or severe nausea in 24 hours) compared with 10% on the chlorpromazine regimen. The median number of vomiting episodes with KYTRIL Injection was 1.5; with chlorpromazine it was 7.0.

Postoperative Nausea and Vomiting

Prevention of Postoperative Nausea and Vomiting

The efficacy of KYTRIL Injection 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 Injection (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 8**). No additional benefit was seen in patients who received the 3 mg dose.

Table 8 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

The efficacy of KYTRIL Injection 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 Injection 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 Injection (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 Injection was more effective than placebo in treating postoperative nausea and vomiting (see **Table 9**). No additional benefit was seen in patients who received the 3 mg dose.

Table 9 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 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.

INDICATIONS AND USAGE

KYTRIL Injection is indicated for:

- The prevention of nausea and/or vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin.
- The prevention and treatment of postoperative nausea and vomiting in adults. 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.

CONTRAINDICATIONS

KYTRIL Injection is contraindicated in patients with known hypersensitivity to the drug or to any of its components.

WARNINGS

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

An adequate QT assessment has not been conducted, but QT prolongation has been reported with KYTRIL. Therefore, Kytril should be used with caution in patients with pre-existing arrhythmias or cardiac conduction disorders, as this might lead to clinical consequences. Patients with cardiac disease, on cardio-toxic chemotherapy, with concomitant electrolyte abnormalities and/or on concomitant medications that prolong the QT interval are particularly at risk.

Drug Interactions

Granisetron does not induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system in vitro. There have been no definitive drug-drug interaction studies to examine pharmacokinetic or pharmacodynamic interaction with other drugs; however, 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. No specific interaction

studies have been conducted in anesthetized patients. In addition, the activity of the cytochrome P-450 subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by KYTRIL in vitro.

In in vitro human microsomal studies, ketoconazole inhibited ring oxidation of KYTRIL. However, the clinical significance of in vivo pharmacokinetic interactions with ketoconazole is not known. In a human pharmacokinetic study, hepatic enzyme induction with phenobarbital resulted in a 25% increase in total plasma clearance of intravenous KYTRIL. The clinical significance of this change is not known.

QT prolongation has been reported with KYTRIL. Use of Kytril in patients concurrently treated with drugs known to prolong the QT interval and/or are arrhythmogenic, this may result in to clinical consequences.

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/m^2/day). The 50 mg/kg/day dose was reduced to 25 mg/kg/day (150 mg/m^2/day) during week 59 due to toxicity. For a 50 kg person of average height (1.46 m^2 body surface area), these doses represent 16, 81 and 405 times the recommended clinical dose (0.37 mg/m^2, iv) 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/m^2/day, 81 times the recommended human dose based on body surface area) and above, and in females treated with 25 mg/kg/day (150 mg/m^2/day, 405 times the recommended human dose based on body surface area). No increase in liver tumors was observed at a dose of 1 mg/kg/day (6 mg/m^2/day, 16 times the recommended human dose based on body surface area) in males and 5 mg/kg/day (30 mg/m^2/day, 81 times the recommended 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/m^2/day, 1622 times the recommended 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, KYTRIL Injection should be prescribed only at the dose and for the indication recommended (see **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION**).

Granisetron was not mutagenic in an 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/m^2/day, 97 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy

Teratogenic Effects

Pregnancy Category B.

Reproduction studies have been performed in pregnant rats at intravenous doses up to 9 mg/kg/day (54 mg/m^2/day, 146 times the recommended human dose based on body surface area) and pregnant rabbits at intravenous doses up to 3 mg/kg/day (35.4 mg/m^2/day, 96 times the recommended human dose based on body surface area) and have 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, this drug should be used during pregnancy only if clearly needed.

Benzyl alcohol may cross the placenta. KYTRIL Injection 1 mg/1 mL is preserved with benzyl alcohol and should be used in pregnancy only if the benefit outweighs the potential risk.

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 Injection is administered to a nursing woman.

Pediatric Use

See **DOSAGE AND ADMINISTRATION** for use in chemotherapy-induced nausea and vomiting in pediatric patients 2 to 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.

Benzyl alcohol, a component of KYTRIL 1 mg/1 mL, has been associated with serious adverse events and death, particularly in neonates. The “gasping syndrome,” characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and metabolites in blood and urine, has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low birth-weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome,” the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low birth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

Geriatric Use

During chemotherapy clinical trials, 713 patients 65 years of age or older received KYTRIL Injection. Effectiveness and safety were similar in patients of various ages.

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.

ADVERSE REACTIONS

QT prolongation has been reported with KYTRIL (see **PRECAUTIONS** and **Drug Interactions**).

Chemotherapy-Induced Nausea and Vomiting

The following have been reported during controlled clinical trials or in the routine management of patients. The percentage figures are based on clinical trial experience only. **Table 10** gives the comparative frequencies of the five most commonly reported adverse events (≥3%) in patients receiving KYTRIL Injection, in single-day chemotherapy trials. These patients received chemotherapy, primarily cisplatin, and intravenous fluids during the 24-hour period following KYTRIL Injection administration. Events were generally recorded over seven days post-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.

Table 10 Principal Adverse Events in Clinical Trials — Single-Day Chemotherapy

	Percent of Patients With Event	
	KYTRIL Injection 40 mcg/kg (n=1268)	**Comparator[1] (n=422)**
Headache	14%	6%
Asthenia	5%	6%
Somnolence	4%	15%
Diarrhea	4%	6%
Constipation	3%	3%

[1] Metoclopramide/dexamethasone and phenothiazines/dexamethasone.

In over 3,000 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 in **Table 10**, were observed; attribution of many of these events to KYTRIL is uncertain.

Hepatic: 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%).

Cardiovascular: 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.

Central Nervous System: 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.

Hypersensitivity: Rare cases of hypersensitivity reactions, sometimes severe (eg, anaphylaxis, shortness of breath, hypotension, urticaria) have been reported.

Other: 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.

Postoperative Nausea and Vomiting

The adverse events listed in **Table 11** were reported in ≥2% of adults receiving KYTRIL Injection 1 mg during controlled clinical trials.

Table 11 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
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 11**. 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%).

Postmarketing Experience

QT prolongation has been reported with KYTRIL (see **PRECAUTIONS** and **Drug Interactions**).

OVERDOSAGE

There is no specific antidote for KYTRIL Injection overdosage. In case of overdosage, symptomatic treatment should be given. Overdosage of up to 38.5 mg of granisetron hydrochloride injection has been reported without symptoms or only the occurrence of a slight headache.

DOSAGE AND ADMINISTRATION

NOTE: KYTRIL 1 MG/1 ML CONTAINS BENZYL ALCOHOL (see **PRECAUTIONS**).

Prevention of Chemotherapy-Induced Nausea and Vomiting

The recommended dosage for KYTRIL Injection is 10 mcg/kg administered intravenously within 30 minutes before initiation of chemotherapy, and only on the day(s) chemotherapy is given.

Infusion Preparation

KYTRIL Injection may be administered intravenously either undiluted over 30 seconds, or diluted with 0.9% Sodium Chloride or 5% Dextrose and infused over 5 minutes.

Stability

Intravenous infusion of KYTRIL Injection should be prepared at the time of administration. However, KYTRIL Injection has been shown to be stable for at least 24 hours when diluted in 0.9% Sodium Chloride or 5% Dextrose and stored at room temperature under normal lighting conditions.

As a general precaution, KYTRIL Injection should not be mixed in solution with other drugs. Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

Pediatric Patients

The recommended dose in pediatric patients 2 to 16 years of age is 10 mcg/kg (see **CLINICAL TRIALS**). Pediatric patients under 2 years of age have not been studied.

Geriatric Patients, Renal Failure Patients or Hepatically Impaired Patients

No dosage adjustment is recommended (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**).

Prevention and Treatment of Postoperative Nausea and Vomiting

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.

Pediatric Patients

Safety and effectiveness of KYTRIL Injection have not been established in pediatric patients for the prevention or treatment of postoperative nausea or vomiting.

Geriatric Patients, Renal Failure Patients or Hepatically Impaired Patients

No dosage adjustment is recommended (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**).

HOW SUPPLIED

KYTRIL Injection, 1 mg/1 mL (free base), is supplied in 1 mL Single-Use Vials and 4 mL Multi-Use Vials. CONTAINS BENZYL ALCOHOL.

NDC 0004-0239-09 (package of 1 Single-Use Vial)
NDC 0004-0240-09 (package of 1 Multi-Use Vial)

KYTRIL Injection, 0.1 mg/1 mL (free base), is supplied in 1 mL Single-Use Vials. CONTAINS NO PRESERVATIVE.

NDC 0004-0242-08 (package of 5 Single-Use Vials)

Storage

Store single-use vials and multi-use vials at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature]

Once the multi-use vial is penetrated, its contents should be used within 30 days.

Do not freeze. Protect from light.

Distributed by:

Pharmaceuticals

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

XXXXXXXX

Revised: September 2009

KYTRIL®

(granisetron hydrochloride)

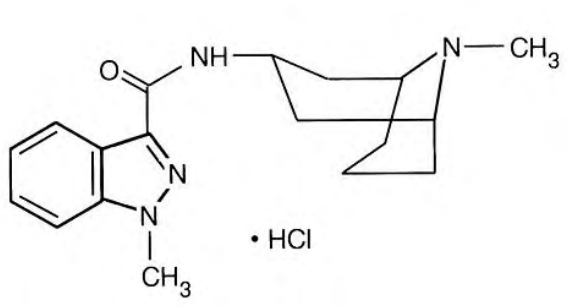
TABLETS

ORAL SOLUTION

R_x only

DESCRIPTION

KYTRIL Tablets and KYTRIL Oral Solution contain granisetron hydrochloride, an antinauseant and antiemetic agent. Chemically it is *endo*-N-(9-methyl-9-azabicyclo [3.3.1] non-3-yl)-1-methyl-1H-indazole-3-carboxamide hydrochloride with a molecular weight of 348.9 (312.4 free base). Its empirical formula is $C_{18}H_{24}N_4O$•HCl, while its chemical structure is:



granisetron hydrochloride

Granisetron hydrochloride is a white to off-white solid that is readily soluble in water and normal saline at 20ºC.

Tablets for Oral Administration

Each white, triangular, biconvex, film-coated KYTRIL Tablet contains 1.12 mg granisetron hydrochloride equivalent to granisetron, 1 mg. Inactive ingredients are: hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

Oral Solution

Each 10 mL of clear, orange-colored, orange-flavored KYTRIL Oral Solution contains 2.24 mg of granisetron hydrochloride equivalent to 2 mg granisetron. Inactive ingredients: citric acid anhydrous, FD&C Yellow No. 6, orange flavor, purified water, sodium benzoate, and sorbitol.

CLINICAL PHARMACOLOGY

Granisetron is a selective 5-hydroxytryptamine$_3$ (5-HT_3) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT_1; 5-HT_{1A}; 5-$HT_{1B/C}$; 5-HT_2; for

alpha$_1$-, alpha$_2$-, or beta-adrenoreceptors; for dopamine-D_2; or for histamine-H_1; benzodiazepine; picrotoxin or opioid receptors.

Serotonin receptors of the 5-HT_3 type are located peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. During chemotherapy that induces vomiting, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT_3 receptors. This evokes vagal afferent discharge, inducing vomiting. Animal studies demonstrate that, in binding to 5-HT_3 receptors, granisetron blocks serotonin stimulation and subsequent vomiting after emetogenic stimuli such as cisplatin. In the ferret animal model, a single granisetron injection prevented vomiting due to high-dose cisplatin or arrested vomiting within 5 to 30 seconds.

In most human studies, granisetron has had little effect on blood pressure, heart rate or ECG. No evidence of an effect on plasma prolactin or aldosterone concentrations has been found in other studies.

Following single and multiple oral doses, KYTRIL Tablets slowed colonic transit in normal volunteers. However, KYTRIL had no effect on oro-cecal transit time in normal volunteers when given as a single intravenous (IV) infusion of 50 mcg/kg or 200 mcg/kg.

Pharmacokinetics

In healthy volunteers and adult cancer patients undergoing chemotherapy, administration of KYTRIL Tablets produced mean pharmacokinetic data shown in **Table 1**.

Table 1 Pharmacokinetic Parameters (Median [range]) Following KYTRIL Tablets (granisetron hydrochloride)

	Peak Plasma Concentration (ng/mL)	Terminal Phase Plasma Half-Life (h)	Volume of Distribution (L/kg)	Total Clearance (L/h/kg)
Cancer Patients 1 mg bid, 7 days (n=27)	5.99 [0.63 to 30.9]	N.D.[1]	N.D.	0.52 [0.09 to 7.37]
Volunteers single 1 mg dose (n=39)	3.63 [0.27 to 9.14]	6.23 [0.96 to 19.9]	3.94 [1.89 to 39.4]	0.41 [0.11 to 24.6]

[1] Not determined after oral administration; following a single intravenous dose of 40 mcg/kg, terminal phase half-life was determined to be 8.95 hours.

N.D. Not determined.

A 2 mg dose of KYTRIL Oral Solution is bioequivalent to the corresponding dose of KYTRIL Tablets (1 mg x 2) and may be used interchangeably.

Absorption

When KYTRIL Tablets were administered with food, AUC was decreased by 5% and C_{max} increased by 30% in non-fasted healthy volunteers who received a single dose of 10 mg.

Distribution

Plasma protein binding is approximately 65% and granisetron distributes freely between plasma and red blood cells.

Metabolism

Granisetron metabolism involves N-demethylation and aromatic ring oxidation followed by conjugation. In vitro liver microsomal studies show that granisetron's major route of metabolism is inhibited by ketoconazole, suggestive of metabolism mediated by the cytochrome P-450 3A subfamily. Animal studies suggest that some of the metabolites may also have 5-HT_3 receptor antagonist activity.

Elimination

Clearance is predominantly by hepatic metabolism. In normal volunteers, approximately 11% of the orally administered dose is eliminated unchanged in the urine in 48 hours. The remainder of the dose is excreted as metabolites, 48% in the urine and 38% in the feces.

Subpopulations

Gender

The effects of gender on the pharmacokinetics of KYTRIL Tablets have not been studied. However, after intravenous infusion of KYTRIL, no difference in mean AUC was found between males and females, although males had a higher C_{max} generally.

In elderly and pediatric patients and in patients with renal failure or hepatic impairment, the pharmacokinetics of granisetron was determined following administration of intravenous KYTRIL.

Elderly

The ranges of the pharmacokinetic parameters in elderly volunteers (mean age 71 years), given a single 40 mcg/kg intravenous dose of KYTRIL Injection, were generally similar to those in younger healthy volunteers; mean values were lower for clearance and longer for half-life in the elderly.

Renal Failure Patients

Total clearance of granisetron was not affected in patients with severe renal failure who received a single 40 mcg/kg intravenous dose of KYTRIL Injection.

Hepatically Impaired Patients

A pharmacokinetic study with intravenous KYTRIL in patients with hepatic impairment due to neoplastic liver involvement showed that total clearance was approximately halved compared to patients without hepatic impairment. Given the wide variability in

pharmacokinetic parameters noted in patients, dosage adjustment in patients with hepatic functional impairment is not necessary.

Pediatric Patients

A pharmacokinetic study in pediatric cancer patients (2 to 16 years of age), given a single 40 mcg/kg intravenous dose of KYTRIL Injection, showed that volume of distribution and total clearance increased with age. No relationship with age was observed for peak plasma concentration or terminal phase plasma half-life. When volume of distribution and total clearance are adjusted for body weight, the pharmacokinetics of granisetron are similar in pediatric and adult cancer patients.

CLINICAL TRIALS

Chemotherapy-Induced Nausea and Vomiting

KYTRIL Tablets prevent nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, as shown by 24-hour efficacy data from studies using both moderately- and highly-emetogenic chemotherapy.

Moderately Emetogenic Chemotherapy

The first trial compared KYTRIL Tablets doses of 0.25 mg to 2 mg twice a day, in 930 cancer patients receiving, principally, cyclophosphamide, carboplatin, and cisplatin (20 mg/m^2 to 50 mg/m^2). Efficacy was based on complete response (ie, no vomiting, no moderate or severe nausea, no rescue medication), no vomiting, and no nausea. **Table 2** summarizes the results of this study.

Table 2 Prevention of Nausea and Vomiting 24 Hours Post-Chemotherapy[1]

	Percentages of Patients KYTRIL Tablet Dose			
Efficacy Measures	**0.25 mg twice a day (n=229) %**	**0.5 mg twice a day (n=235) %**	**1 mg twice a day (n=233) %**	**2 mg twice a day (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.
*Statistically significant (P<0.01) vs. 0.25 mg bid.
†Statistically significant (P<0.01) vs. 0.5 mg bid.

Results from a second double-blind, randomized trial evaluating KYTRIL Tablets 2 mg once a day and KYTRIL Tablets 1 mg twice a day were compared to prochlorperazine 10 mg twice a day derived from a historical control. At 24 hours, there was no statistically significant difference in efficacy between the two KYTRIL Tablet regimens. Both regimens were statistically superior to the prochlorperazine control regimen (see **Table 3**).

Table 3 Prevention of Nausea and Vomiting 24 Hours Post-Chemotherapy[1]

Efficacy Measures	Percentages of Patients		
	KYTRIL Tablets 1 mg twice a day (n = 354) %	**KYTRIL Tablets 2 mg once a day (n = 343) %**	**Prochlorperazine[2] 10 mg twice daily (n=111) %**
Complete Response[3]	69*	64*	41
No Vomiting	82*	77*	48
No Nausea	51*	53*	35
Total Control[4]	51*	50*	33

1 Moderately emetogenic chemotherapeutic agents included cisplatin (20 mg/m^2 to 50 mg/m^2), oral and intravenous cyclophosphamide, carboplatin, dacarbazine, doxorubicin.
2 Historical control from a previous double-blind KYTRIL trial.
3 No vomiting, no moderate or severe nausea, no rescue medication.
4 No vomiting, no nausea, no rescue medication.
*Statistically significant (P<0.05) vs. prochlorperazine historical control.

Results from a KYTRIL Tablets 2 mg daily alone treatment arm in a third double-blind, randomized trial, were compared to prochlorperazine (PCPZ), 10 mg bid, derived from a historical control. The 24-hour results for KYTRIL Tablets 2 mg daily were statistically superior to PCPZ for all efficacy parameters: complete response (58%), no vomiting (79%), no nausea (51%), total control (49%). The PCPZ rates are shown in **Table 3**.

Cisplatin-Based Chemotherapy

The first double-blind trial compared KYTRIL Tablets 1 mg bid, relative to placebo (historical control), in 119 cancer patients receiving high-dose cisplatin (mean dose 80 mg/m^2). At 24 hours, KYTRIL Tablets 1 mg bid was significantly (P<0.001) superior to placebo (historical control) in all efficacy parameters: complete response (52%), no

vomiting (56%) and no nausea (45%). The placebo rates were 7%, 14%, and 7%, respectively, for the three efficacy parameters.

Results from a KYTRIL Tablets 2 mg once a day alone treatment arm in a second double-blind, randomized trial, were compared to both KYTRIL Tablets 1 mg twice a day and placebo historical controls. The 24-hour results for KYTRIL Tablets 2 mg once a day were: complete response (44%), no vomiting (58%), no nausea (46%), total control (40%). The efficacy of KYTRIL Tablets 2 mg once a day was comparable to KYTRIL Tablets 1 mg twice a day and statistically superior to placebo. The placebo rates were 7%, 14%, 7%, and 7%, respectively, for the four parameters.

No controlled study comparing granisetron injection with the oral formulation to prevent chemotherapy-induced nausea and vomiting has been performed.

Radiation-Induced Nausea and Vomiting

Total Body Irradiation

In a double-blind randomized study, 18 patients receiving KYTRIL Tablets, 2 mg daily, experienced significantly greater antiemetic protection 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 three fractions on each of the first 3 days, and two fractions on the fourth day. KYTRIL Tablets were given one hour before the first radiation fraction of each day.

Twenty-two percent (22%) of patients treated with KYTRIL Tablets did not experience vomiting or receive rescue antiemetics over the entire 4-day dosing period, compared to 0% of patients in the historical negative control group ($P<0.01$).

In addition, 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 Tablets, 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.

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 superior to placebo in patients receiving up to 10 daily fractions of radiation, but was not superior to 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 provided significantly greater protection from nausea and vomiting than placebo.

INDICATIONS AND USAGE

KYTRIL (granisetron hydrochloride) is indicated for the prevention of:

- Nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin.
- Nausea and vomiting associated with radiation, including total body irradiation and fractionated abdominal radiation.

CONTRAINDICATIONS

KYTRIL is contraindicated in patients with known hypersensitivity to the drug or any of its components.

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.

An adequate QT assessment has not been conducted, but QT prolongation has been reported with KYTRIL. Therefore, Kytril should be used with caution in patients with pre-existing arrhythmias or cardiac conduction disorders, as this might lead to clinical consequences. Patients with cardiac disease, on cardio-toxic chemotherapy, with concomitant electrolyte abnormalities and/or on concomitant medications that prolong the QT interval are particularly at risk.

Drug Interactions

Granisetron does not induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system in vitro. There have been no definitive drug-drug interaction studies to examine pharmacokinetic or pharmacodynamic interaction with other drugs; however, 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. No specific interaction studies have been conducted in anesthetized patients. In addition, the activity of the cytochrome P-450 subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by KYTRIL in vitro.

In in vitro human microsomal studies, ketoconazole inhibited ring oxidation of KYTRIL. However, the clinical significance of in vivo pharmacokinetic interactions with ketoconazole is not known. In a human pharmacokinetic study, hepatic enzyme induction

with phenobarbital resulted in a 25% increase in total plasma clearance of intravenous KYTRIL. The clinical significance of this change is not known.

QT prolongation has been reported with KYTRIL. Use of Kytril in patients concurrently treated with drugs known to prolong the QT interval and/or are arrhythmogenic, this may result in clinical consequences.

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/m^2/day). The 50 mg/kg/day dose was reduced to 25 mg/kg/day (150 mg/m^2/day) during week 59 due to toxicity. For a 50 kg person of average height (1.46 m^2 body surface area), these doses represent 4, 20, and 101 times the recommended clinical dose (1.48 mg/m^2, oral) 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/m^2/day, 20 times the recommended human dose based on body surface area) and above, and in females treated with 25 mg/kg/day (150 mg/m^2/day, 101 times the recommended human dose based on body surface area). No increase in liver tumors was observed at a dose of 1 mg/kg/day (6 mg/m^2/day, 4 times the recommended human dose based on body surface area) in males and 5 mg/kg/day (30 mg/m^2/day, 20 times the recommended 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/m^2/day, 405 times the recommended 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, KYTRIL (granisetron hydrochloride) should be prescribed 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 oral doses up to 100 mg/kg/day (600 mg/m^2/day, 405 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy

Teratogenic Effects

Pregnancy Category B.

Reproduction studies have been performed in pregnant rats at oral doses up to 125 mg/kg/day (750 mg/m^2/day, 507 times the recommended human dose based on body surface area) and pregnant rabbits at oral doses up to 32 mg/kg/day (378 mg/m^2/day, 255

times the recommended human dose based on body surface area) and have 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, this drug should be used 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 Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

During clinical trials, 325 patients 65 years of age or older received KYTRIL Tablets; 298 were 65 to 74 years of age, and 27 were 75 years of age or older. Efficacy and safety were maintained with increasing age.

ADVERSE REACTIONS

QT prolongation has been reported with KYTRIL (see **PRECAUTIONS** and **Drug Interactions**).

Chemotherapy-Induced Nausea and Vomiting

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 daily for 1 day, adverse experiences reported in more than 5% of the patients with comparator and placebo incidences are listed in **Table 4**.

Table 4 Principal Adverse Events in Clinical Trials

	Percent of Patients With Event			
	KYTRIL[1] Tablets 1 mg twice a day (n=978)	**KYTRIL[1] Tablets 2 mg once a day (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%

[1] Adverse 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.

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

Other adverse events reported in clinical trials were:

Gastrointestinal: 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.

Hepatic: 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 comparators (AST: 2%; ALT: 9%).

Cardiovascular: Hypertension (1%); hypotension, angina pectoris, atrial fibrillation, and syncope have been observed rarely.

Central Nervous System: 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.

Hypersensitivity: Rare cases of hypersensitivity reactions, sometimes severe (eg, anaphylaxis, shortness of breath, hypotension, urticaria) have been reported.

Other: Fever (5%). Events often associated with chemotherapy also have been reported: leukopenia (9%), decreased appetite (6%), anemia (4%), alopecia (3%), thrombocytopenia (2%).

Over 5000 patients have received injectable KYTRIL in clinical trials.

Table 5 gives the comparative frequencies of the five commonly reported adverse events (≥3%) in patients receiving KYTRIL Injection, 40 mcg/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 5 Principal Adverse Events in Clinical Trials — Single-Day Chemotherapy

	Percent of Patients with Event	
	KYTRIL Injection[1] 40 mcg/kg (n=1268)	**Comparator[2] (n=422)**
Headache	14%	6%
Asthenia	5%	6%
Somnolence	4%	15%
Diarrhea	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.

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.

Postmarketing Experience

QT prolongation has been reported with KYTRIL (see **PRECAUTIONS** and **Drug Interactions**).

OVERDOSAGE

There is no specific treatment for granisetron hydrochloride overdosage. In case of overdosage, symptomatic treatment should be given. Overdosage of up to 38.5 mg of granisetron hydrochloride injection has been reported without symptoms or only the occurrence of a slight headache.

DOSAGE AND ADMINISTRATION

Emetogenic Chemotherapy

The recommended adult dosage of oral KYTRIL (granisetron hydrochloride) is 2 mg once daily or 1 mg twice daily. In the 2 mg once-daily regimen, two 1 mg tablets or 10 mL of KYTRIL Oral Solution (2 teaspoonfuls, equivalent to 2 mg of granisetron) are given up to 1 hour before chemotherapy. In the 1 mg twice-daily regimen, the first 1 mg tablet or one teaspoonful (5 mL) of KYTRIL Oral Solution is given up to 1 hour before chemotherapy, and the second tablet or second teaspoonful (5 mL) of KYTRIL Oral Solution, 12 hours after the first. Either regimen is administered only on the day(s) chemotherapy is given. Continued treatment, while not on chemotherapy, has not been found to be useful.

Use in the Elderly, Renal Failure Patients or Hepatically Impaired Patients

No dosage adjustment is recommended (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**).

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Radiation (Either Total Body Irradiation or Fractionated Abdominal Radiation)

The recommended adult dosage of oral KYTRIL is 2 mg once daily. Two 1 mg tablets or 10 mL of KYTRIL Oral Solution (2 teaspoonfuls, equivalent to 2 mg of granisetron) are taken within 1 hour of radiation.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in the Elderly

No dosage adjustment is recommended.

HOW SUPPLIED

Tablets

White, triangular, biconvex, film-coated tablets; tablets are debossed K1 on one face.

1 mg Unit of Use 2’s: NDC 0004-0241-33

1 mg Single Unit Package 20’s: NDC 0004-0241-26 (intended for institutional use only)

Storage

Store between 15º and 30ºC (59º and 86ºF). Keep container closed tightly. Protect from light.

KYTRIL® (granisetron hydrochloride)

Oral Solution

Clear, orange-colored, orange-flavored, 2 mg/10 mL, in 30 mL amber glass bottles with child-resistant closures: NDC 0004-0237-09

Storage

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Keep bottle closed tightly and stored in an upright position. Protect from light.

Distributed by:

Pharmaceuticals

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

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