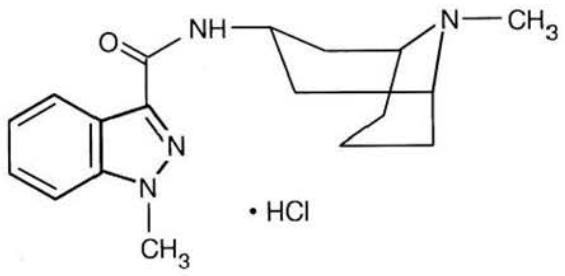
KYTRIL®
(granisetron hydrochloride)
Injection

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 $C_{18}H_{24}N_4O \cdot HCl$, 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 is available in 1 mL single-dose and 4 mL multi-dose vials.

Single-Dose Vials

Each 1 mL of preservative-free aqueous solution contains 1.12 mg granisetron hydrochloride equivalent to granisetron, 1 mg and sodium chloride, 9 mg. The solution's pH ranges from 4.7 to 7.3.

Multi-Dose Vials

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.

CLINICAL PHARMACOLOGY

Granisetron is a selective 5-hydroxytryptamine3 (5-HT3) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT1; 5-HT1A; 5-HT1B/C; 5-HT2; for alpha1-, alpha2- or beta-adrenoreceptors; for dopamine-D2; or for histamine-H1; benzodiazepine; picrotoxin or opioid receptors.

Serotonin receptors of the 5-HT3 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-
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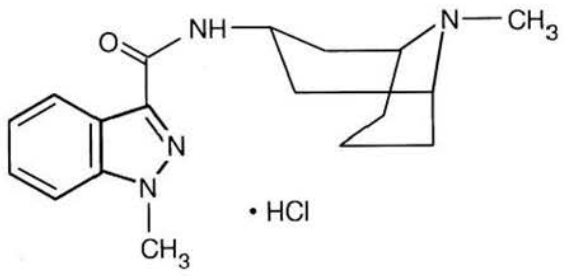

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Serotonin receptors of the 5-HT3 type are located peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. During chemotherapy-induced vomiting, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT3 receptors. This evokes vagal afferent discharge and may induce vomiting. Animal studies demonstrate that, in binding to 5-

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.

Geriatrics

The ranges of the pharmacokinetic parameters in geriatric 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 geriatric 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 and the good tolerance of doses well above the recommended 10 mcg/kg dose, dosage adjustment in patients with possible 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.

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