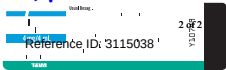




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Elderly

The ranges of the pharmacokinetic parameters in elderly volunteers (mean age 71 years), given a single 40 mcg/kg intravenous dose of granisetron hydrochloride 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 3).

Pediatric Patients

A pharmacokinetic study in pediatric cancer patients (2 to 16 years of age), given a single 40 mcg/kg intravenous dose of granisetron hydrochloride 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 granisetron hydrochloride 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.

13 NONCLINICAL TOXICOLOGY

13.1 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 clinical dose (0.37 mg/m², 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/m²/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/m²/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/m²/day, 16 times the recommended human dose based on body surface area) in males and 5 mg/kg/day (30 mg/m²/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/m²/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, granisetron hydrochloride injection should be prescribed only at the dose and for the indication recommended [see *Indications and Usage (1)* and *Dosage and Administration (2)*].

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/m²/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.

14 CLINICAL STUDIES

14.1 Chemotherapy-Induced Nausea and Vomiting

Single-Day Chemotherapy

Cisplatin-Based Chemotherapy

In a double-blind, placebo-controlled study in 28 cancer patients, granisetron hydrochloride 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 5).

Table 5 Prevention of Chemotherapy-Induced Nausea and Vomiting — Single-Day Cisplatin Therapy^a

	Granisetron Hydrochloride Injection	Placebo	P-Value
Number of Patients	14	14	
Response Over 24 Hours			
Complete Response ^b	93%	7%	<0.001
No Vomiting	93%	14%	<0.001
No More Than Mild Nausea	93%	7%	<0.001

^a Cisplatin administration began within 10 minutes of granisetron hydrochloride injection infusion and continued for 1.5 to 3.0 hours. Mean cisplatin dose was 86 mg/m² in the granisetron hydrochloride injection group and 80 mg/m² in the placebo group.

^b No vomiting and no moderate or severe nausea.

Granisetron hydrochloride injection was also evaluated in a randomized dose response study of cancer patients receiving cisplatin ≥75 mg/m². Additional chemotherapeutic agents included: anthracyclines, carboplatin, cytostatic antibiotics, folic acid derivatives, methylhydrazine, nitrogen mustard analogs, podophyllotoxin derivatives, pyrimidine analogs, and vinca alkaloids. Granisetron hydrochloride 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 6).

Table 6 Prevention of Chemotherapy-Induced Nausea and Vomiting — Single-Day High-Dose Cisplatin Therapy^a

	Granisetron Hydrochloride 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 ^b	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

^a Cisplatin administration began within 10 minutes of granisetron hydrochloride injection infusion and continued for 2.6 hours (mean). Mean cisplatin doses were 96 to 99 mg/m².

^b No vomiting and no moderate or severe nausea.

Granisetron hydrochloride injection was also evaluated in a double-blind, randomized dose response study of 353 patients stratified for high (≥80 to 120 mg/m²) or low (50 to 79 mg/m²) cisplatin dose. Response rates of patients for both cisplatin strata are given in Table 7.

Table 7 Prevention of Chemotherapy-Induced Nausea and Vomiting — Single-Day High-Dose and Low-Dose Cisplatin Therapy^a

	Granisetron Hydrochloride 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 ^b	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 ^b	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

^a Cisplatin administration began within 10 minutes of granisetron hydrochloride injection infusion and continued for 2 hours (mean). Mean cisplatin doses were 64 and 98 mg/m² for low and high strata.

^b 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

Granisetron hydrochloride 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/m², cisplatin 20 to 50 mg/m² and cyclophosphamide >600 mg/m². Granisetron hydrochloride injection was superior to the chlorpromazine regimen in preventing nausea and vomiting (see Table 8).

Table 8 Prevention of Chemotherapy-Induced Nausea and Vomiting— Single-Day Moderately Emetogenic Chemotherapy

	Granisetron Hydrochloride Injection	Chlorpromazine ^a	P-Value
Number of Patients	133	133	
Response Over 24 Hours			
Complete Response ^b	68%	47%	<0.001
No Vomiting	73%	53%	<0.001
No More Than Mild Nausea	77%	59%	<0.001

^a Patients also received dexamethasone, 12 mg.

^b No vomiting and no moderate or severe nausea.

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

Repeat-Cycle Chemotherapy

In an uncontrolled trial, 512 cancer patients received granisetron hydrochloride 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. Granisetron hydrochloride 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 granisetron hydrochloride injection 10, 20 or 40 mcg/kg. Patients were treated with cisplatin ≥60 mg/m², cytarabine ≥3 g/m², cyclophosphamide ≥1 g/m² or nitrogen mustard ≥6 mg/m² (see Table 9).

Table 9 Prevention of Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients

	Granisetron Hydrochloride 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 ^a	21%	31%	32%

^a No vomiting and no moderate or severe nausea.

A second pediatric study compared granisetron hydrochloride injection 20 mcg/kg to chlorpromazine plus dexamethasone in 88 patients treated with ifosfamide ≥3 g/m²/day for two or three days. Granisetron hydrochloride injection was administered on each day of ifosfamide treatment. At 24 hours, 22% of granisetron hydrochloride 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 granisetron hydrochloride injection was 1.5; with chlorpromazine it was 7.0.

16 HOW SUPPLIED/STORAGE AND HANDLING

Granisetron hydrochloride injection USP is supplied as follows:

NDC Number	Contents	Package size
0703-7973-01	4 mg/4 mL (free base)	4 mL multi-use vial packaged individually

Storage

Store multi-use vial 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. Retain in carton until time of use.

17 PATIENT COUNSELING INFORMATION

Patients should be informed that the most common adverse reactions for the indication of chemotherapy induced nausea and vomiting are headache and constipation (see Table 1).

Patients should be advised of the risk of allergic reactions if they have a prior allergic reaction to a class of antiemetics known as 5-HT₃ receptor antagonists.

Electrocardiogram changes (QT prolongation) have been reported with the use of granisetron hydrochloride. Patients should be cautioned about the use of this drug if they have heart problems or take medications for heart problems.

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Teva Pharmaceuticals USA

Sellersville, PA 18960