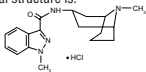


Gransetron HCl Injection

DESCRIPTION
Gransetron hydrochloride injection is an antiemetic and antiemetic agent. Chemically it is *trans*-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 (32.4 free base). Its empirical formula is $C_{19}H_{20}N_4O \cdot HCl$, while its chemical structure is:



Gransetron hydrochloride is a white to off-white solid that is readily soluble in water and normal saline at 20°C. Gransetron hydrochloride injection is a clear, colorless, sterile, nonpyrogenic, aqueous solution for intravenous administration. Gransetron hydrochloride injection 1 mg/1 mL is available in a 4 mL multi-use vial. Each 1 mL contains 1.12 mg gransetron hydrochloride equivalent to gransetron 1 mg; sodium chloride, 9 mg; citric acid, 2 mg; methylparaben, 1.8 mg and propylparaben, 0.2 mg, as preservatives, sodium hydroxide and hydrochloric acid, as pH adjusters. The solution's pH ranges from 4.0 to 6.0.

CLINICAL PHARMACOLOGY

Gransetron is a selective 5-hydroxytryptamine₂ (5-HT₂) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT₁; 5-HT_{1A}; 5-HT_{1B}; 5-HT₂; for alpha₁, alpha₂, or beta-adrenoreceptors; for dopamine-D₁; or for histamine-H₁; benzodiazepine; picrotoxin or opioid receptors. Serotonin receptors of the 5-HT₂ 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-HT₂ receptors. This evokes vagal afferent discharge and may induce vomiting. Animal studies demonstrate that, in binding to 5-HT₂ receptors, gransetron blocks serotonin stimulation and subsequent vomiting after emetogenic stimuli such as cisplatin. In the ferret animal model, a single gransetron injection prevented vomiting due to high-dose cisplatin or arrested vomiting within 5 to 30 seconds.

In most human studies, gransetron has had little effect on blood pressure, heart rate or ECG. Gransetron had no effect on plasma prolactin or aldosterone concentrations has been found in other studies.

Gransetron hydrochloride injection exhibited no effect on oro-caecal 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 gransetron hydrochloride 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 Gransetron Hydrochloride 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 gransetron distributes freely between plasma and red blood cells.

Metabolism

Gransetron metabolism involves N-demethylation and aromatic ring oxidation followed by conjugation. *In vitro* liver microsomal studies show that gransetron'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-HT₂ 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 gransetron 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 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 gransetron 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 gransetron are similar in pediatric and adult cancer patients.

Renal Failure Patients

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

CLINICAL TRIALS

Chemotherapy-Induced Nausea and Vomiting

Single-Day Chemotherapy

Cisplatin-Based Chemotherapy
In a double-blind, placebo-controlled study in 28 cancer patients, gransetron 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 2).

Table 2. Prevention of Chemotherapy-Induced Nausea and Vomiting — Single-Day Cisplatin Therapy¹

	Gransetron Hydrochloride Injection	Placebo	P-Value
Number of Patients	14	14	
Response Over 24 Hours	93%	7%	<0.001
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 gransetron hydrochloride injection infusion and continued for 1.5 to 3 hours. Mean cisplatin dose was 86 mg/m² in the gransetron hydrochloride injection group and 80 mg/m² in the placebo group.

² No vomiting and no moderate or severe nausea. Gransetron 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, podophylotoxin derivatives, pyrimidine analogs, and vinca alkaloids. Gransetron 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 3).

Table 3. Prevention of Chemotherapy-Induced Nausea and Vomiting — Single-Day High-Dose Cisplatin Therapy¹

	Gransetron 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 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 gransetron hydrochloride injection infusion and continued for 2.6 hours (mean). Mean cisplatin doses were 96 to 99 mg/m².

² No vomiting and no moderate or severe nausea. Gransetron 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 4.

Table 4. Prevention of Chemotherapy-Induced Nausea and Vomiting — Single-Day High-Dose and Low-Dose Cisplatin Therapy¹

	Gransetron 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 ²	18%	41%	40%	47%	0.018	0.025	0.004
No Vomiting	28%	47%	44%	53%	NS	NS	0.016
No Nausea	15%	39%	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 gransetron hydrochloride injection infusion and continued for 2 hours (mean). Mean cisplatin doses were 64 and 98 mg/m² 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

Gransetron 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. Gransetron hydrochloride injection was superior to the chlorpromazine regimen in preventing nausea and vomiting (see Table 5).

Table 5. Prevention of Chemotherapy-Induced Nausea and Vomiting — Single-Day Moderately Emetogenic Chemotherapy

	Gransetron Hydrochloride 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 gransetron hydrochloride injection doses of 40 mcg/kg and 160 mcg/kg.

Repeat-Cycle Chemotherapy

In an uncontrolled trial, 512 cancer patients received gransetron 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. Gransetron 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 gransetron 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 6).

Table 6. Prevention of Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients

	Gransetron 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 ¹	21%	31%	32%

¹ No vomiting and no moderate or severe nausea. A second pediatric study compared gransetron hydrochloride injection 20 mcg/kg to chlorpromazine plus dexamethasone in 88 patients treated with ifosfamide ≥3 g/m²/day for two or three days. Gransetron hydrochloride injection was administered on each day of ifosfamide treatment. At 24 hours, 22% of gransetron 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 gransetron hydrochloride injection was 1.5; with chlorpromazine it was 7.0.

INDICATIONS AND USAGE

Gransetron hydrochloride injection is indicated for:
• The prevention of nausea and/or vomiting associated with initial and repeat courses of moderately emetogenic cancer therapy, including high-dose cisplatin.

CONTRAINDICATIONS

Gransetron hydrochloride 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-HT₂ receptor antagonists.

PRECAUTIONS
Gransetron hydrochloride injection is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction. The use of gransetron hydrochloride injection in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distention.

Drug Interactions

Gransetron 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, gransetron hydrochloride injection has been safely administered with drugs representing benzodiazepines, neuroleptics and anti-ulcer medications commonly prescribed with antiemetic treatments. Gransetron hydrochloride injection also does not appear to interact with emetogenic cancer chemotherapies. Because gransetron 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 gransetron. No specific interaction studies have been conducted in anesthetized patients. In addition, the activity of the cytochromes P-450 subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by gransetron hydrochloride injection *in vitro*.

In *in vitro* human microsomal studies, ketoconazole inhibited ring oxidation of gransetron hydrochloride injection. 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 gransetron hydrochloride injection. The clinical significance of this change is not known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month carcinogenicity study, rats were treated orally with gransetron 1, 5 or 50 mg/kg/day (6, 30 or 300 mg/m²/day). The 30 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) and above. 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 gransetron 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 gransetron did not show a statistically significant increase in tumor incidence, but the study was not conclusive. Because of the mor' findings in rat studies, gransetron hydrochloride injection should be prescribed only at the dose and for the indication recommended (see INDICATIONS AND USAGE AND DOSAGE AND ADMINISTRATION).

Gransetron 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.

Gransetron 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.

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/m²/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/m²/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 gransetron. 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 gransetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when gransetron hydrochloride 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.

Geriatric Use

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

ADVERSE REACTIONS

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 7 gives the comparative frequencies of the five most commonly reported adverse events (≥3% in patients receiving gransetron hydrochloride injection, in single-day chemotherapy trials. Patients receiving chemotherapy, primarily cisplatin, and intravenous fluids during the 24-hour period following gransetron hydrochloride injection administration. Events were generally recorded over seven days post-gransetron hydrochloride injection administration. In the absence of a placebo group, there is uncertainty as to how many of these events should be attributed to gransetron hydrochloride injection, except for headache, which was clearly more frequent than in comparison groups.

Table 7. Principal Adverse Events in Clinical Trials — Single-Day Chemotherapy

	Percent of Patients With Event	
	Gransetron Hydrochloride 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 gransetron hydrochloride 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 7, were observed; attribution of many of these events to gransetron hydrochloride injection is uncertain.

Other Events
In comparative trials with cisplatin regimens, elevations of AST and ALT (>2 times the upper limit of normal) following administration of gransetron hydrochloride 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 gransetron hydrochloride injection (8.6%) than with comparative drugs (3.4%, P<0.014), which usually included dexamethasone.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

Prevention of Chemotherapy-Induced Nausea and Vomiting
The recommended dosage for gransetron hydrochloride 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

Gransetron hydrochloride 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 gransetron hydrochloride injection should be prepared at the time of administration. However, gransetron hydrochloride 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, gransetron hydrochloride 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