PRODUCT MONOGRAPH

[Pr]Granisetron Hydrochloride Injection

sterile

1 mg/mL granisetron as hydrochloride,

1 mL, 3 mL and 4 mL vials

Antiemetic
(5-HT_3 receptor antagonist)

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
i.v. injection	1 mL, 3 mL and 4 mL vials, 1 mg/mL injection	Benzyl alcohol *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USES

Granisetron Hydrochloride Injection is indicated for:

Adults

- The prevention of nausea and vomiting associated with emetogenic cancer chemotherapy, including high dose cisplatin.

Geriatrics (>65 years of age)

Chemotherapy-induced Nausea and Vomiting

Safety and efficacy of Granisetron Hydrochloride appear to be similar to that observed in younger adults (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Pediatrics

Safety and efficacy of Granisetron Hydrochloride has not been adequately studied in children or adolescents under 18 years of age and it is not indicated for use in this population (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Granisetron Hydrochloride Injection is contraindicated in patients with a known hypersensitivity to the drug or to any component of its formulations.

WARNINGS AND PRECAUTIONS

Carcinogenesis and Mutagenesis

Granisetron hydrochloride has been associated with an increased occurrence of hepatocellular tumours in carcinogenicity studies performed in rodents at doses in excess of the recommended human dose. Although the clinical significance of these findings has not been determined, the use of this drug should be restricted to the treatment of nausea and vomiting in patients undergoing emetogenic cancer chemotherapy. The recommended dosage of granisetron hydrochloride should not be exceeded.

Granisetron was administered to rats in the diet in a 24 month carcinogenicity study. The incidence of hepatocellular carcinomas and adenomas was significantly increased in male rats treated at doses of 5 mg/kg/day and in rats of both sexes treated with 25 mg/kg/day. No increase in the rate of occurrence of liver tumours was observed in the 1 mg/kg/day treatment group (100 times the recommended human dose given intravenously).

In another 24 month carcinogenicity study, mice were administered granisetron in the diet at doses of 1, 5, and 50 mg/kg/day. There was a statistically significant increase in the incidence of hepatocellular carcinomas in males and hepatocellular adenomas in females dosed with 50 mg/kg/day. No statistically significant increase in liver tumours was observed in mice at a dose of 5 mg/kg/day (500 times the recommended human dose given intravenously).

Gastrointestinal

Granisetron hydrochloride is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction. The use of granisetron hydrochloride in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distention. Patients with signs of sub-acute intestinal obstruction should be monitored following administration of granisetron hydrochloride.

Sensitivity/Resistance

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

Special Populations

Pregnant Women: The use of granisetron hydrochloride in pregnant women has not been studied and is not recommended. Reproduction studies performed in pregnant rats given granisetron at intravenous dosages up to 9 mg/kg/day and pregnant rabbits at intravenous dosage up to 3 mg/kg/day revealed no evidence of impaired fertility or harm to the fetus due to granisetron (see TOXICOLOGY, **Reproduction**).

Nursing Women: It is not known whether granisetron is excreted in human milk. Nursing is not recommended during treatment with granisetron hydrochloride.

Pediatrics: The safety and efficacy of granisetron hydrochloride has not been adequately studied in children or adolescents under 18 years of age (see INDICATIONS AND CLINICAL USES and DOSAGE AND ADMINISTRATION).

Geriatrics (> *65* years of age): During clinical trials, 713 patients 65 years of age or older received intravenous granisetron hydrochloride and of 325 patients 65 years of age or older who received oral granisetron hydrochloride, 298 were 65 to 74 years of age and 27 were 75 years of age or older. The efficacy and safety of granisetron hydrochloride did not appear to be age dependent (see INDICATIONS AND CLINICAL USES and DOSAGE AND ADMINISTRATION).

Information for Patients

Effect on Ability to Drive and Use Machinery

In healthy subjects, no clinically relevant effects on resting EEG or on the performance of psychometric tests were observed after i.v. granisetron hydrochloride at any dose tested (up to 200 mcg/kg). There are no data on the effect of granisetron hydrochloride on the ability to drive. As there have been occasional reports of somnolence in clinical studies, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that the drug treatment does not affect them adversely.

ADVERSE REACTIONS

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Drug Reaction Overview

The most common adverse events reported by patients receiving intravenous granisetron hydrochloride in single-day chemotherapy trials are: headache, asthenia, somnolence, diarrhea, constipation, and abdominal pain (see Table 1 for the percentages of patients with these events). The only two common adverse experiences recognized to be causally related to granisetron hydrochloride are constipation and headache.

Clinical Trial Adverse Drug Reactions

Chemotherapy-induced Nausea and Vomiting

Intravenous granisetron hydrochloride was given as a single dose. Patients received cancer chemotherapy which consisted primarily of cisplatin or cyclophosphamide regimens. During the 24-hour period following intravenous administration of granisetron hydrochloride, i.v. fluids were also given. Adverse events were recorded over seven days when granisetron hydrochloride was given on a single day. In the absence of a placebo group, the relationship of observed adverse events to treatment with granisetron hydrochloride is difficult to judge.

Table 1 gives the frequencies of the six adverse events most commonly reported by patients receiving intravenous granisetron hydrochloride in single-day chemotherapy trials. This table does not include those events that are commonly associated with chemotherapy or the underlying malignant disease.

Table 1. Principal Adverse Events in Clinical Trials of Single-Day Chemotherapy

	Percentage of Patients with Event **Intravenous granisetron hydrochloride** **(10-40 mcg/kg)** **(n=1519)**
Headache	14%
Asthenia	5%
Somnolence	4%
Diarrhea	5%
Constipation	4%
Abdominal Pain	3%

The only two common adverse experiences recognized to be causally related to granisetron hydrochloride are constipation and headache. As with other drugs of this class, rare cases of hypersensitivity reactions, sometimes severe (e.g. anaphylaxis, shortness of breath, hypotension, urticaria) have been reported.

Less Common Clinical Trial Adverse Drug Reactions (≤1%)

Chemotherapy-induced Nausea and Vomiting

The safety profile of granisetron hydrochloride has been evaluated in 3,269 patients receiving intravenous granisetron hydrochloride (2 to 160 mcg/kg) and 2,600 patients receiving oral granisetron (0.25 - 20 mg) in single-day and multiple-day clinical trials with emetogenic cancer

therapies. In the listings which follow, a COSTART-based dictionary terminology has been used to classify reported adverse experiences. The frequencies presented, therefore, represent the proportion of the patients who experienced an event of the type cited on at least one occasion while receiving granisetron hydrochloride.

Experiences are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions:

frequent experiences are defined as: those occurring on one or more occasion in at least 1/100 patients

infrequent adverse experiences as: those occurring in less than 1/100 but at least 1/1000 patients

rare experiences as: those occurring in less than 1/1000 patients

Many adverse experiences are observed in cancer chemotherapy patients. All adverse experiences are included except those for which the drug cause was remote, those reported in terms so general as to be uninformative and those already listed in Table 1.

Body As A Whole:	**Frequent:**	Abdominal pain
	Infrequent:	Abdomen enlarged, chills, fever, malaise
	Rare:	Allergic reaction, chest pain
Cardiovascular System:	**Infrequent:**	Hypertension, hypotension, migraine, syncope, vasodilatation
	Rare:	Arrhythmia, bradycardia, palpitation, postural hypotension, tachycardia, ventricular arrhythmia, angina pectoris, and atrial fibrillation
Gastrointestinal System:	**Frequent:**	Decreased appetite
	Infrequent:	Dry mouth, dyspepsia, flatulence, jaundice, liver function tests abnormal [Elevation of AST and ALT (>2 times the upper limit of normal)], nausea
	Rare:	Gastrointestinal haemorrhage, hepatic coma, ileus, liver damage, melena, vomiting
Hemic and Lymphatic System:	**Rare:**	Coagulation time increased, eosinophilia, leukopenia, anemia, thrombocytopenia

Metabolic and Nutritional:	**Infrequent:**	Hypokalemia
	Rare:	Bilirubinemia, edema, hyperphosphatemia, hyponatremia
Nervous System:	**Infrequent:**	Agitation, anxiety, dizziness, drugged feeling, insomnia, nervousness, paresthesia, tremor
	Rare:	Coma, depersonalisation, grand mal convulsion, vertigo
Respiratory System:	**Infrequent:**	Dyspnea, hiccup
	Rare:	Epistaxis, rhinitis, sinusitis
Skin and Appendages:	**Infrequent:**	Pruritus, rash, sweating
	Rare:	Photosensitivity
Special Searches:	**Rare:**	Puncture site pain
Special Senses:	**Infrequent:**	Taste perversion
	Rare:	Abnormal vision
Urogenital System:	**Infrequent:**	Dysuria
	Rare:	Urinary incontinence

DRUG INTERACTIONS

Overview

No pharmacodynamic interaction was found between single 160 mcg/kg i.v. doses of granisetron and single oral doses of 2.5 mg lorazepam or 3 mg haloperidol. Pharmacokinetic interactions with these drugs were not investigated.

The pharmacokinetic characteristics of a single 40 mcg/kg i.v. dose of granisetron were not significantly different whether it was administered alone or following 8 days of treatment with the hepatic enzyme inhibitor, cimetidine (200 mg q.i.d.).

Granisetron does not induce or inhibit the cytochrome P_{450} drug metabolizing enzyme system.

DOSAGE AND ADMINISTRATION

Recommended Dose, Dosage Adjustment and Administration

Emetogenic Chemotherapy

Adults: The recommended dosage of Granisetron Hydrochloride Injection is 10 mcg/kg infused intravenously over 5 minutes, beginning within 30 minutes before initiation of chemotherapy only on the day(s) when chemotherapy is given (see **Reconstitution** instructions).

Geriatrics: Available clinical data suggest that dosage reductions may not be necessary in this patient population (see INDICATIONS AND CLINICAL USES and WARNINGS AND PRECAUTIONS).

Pediatrics: See INDICATIONS AND CLINICAL USES and WARNINGS AND PRECAUTIONS.

Renally impaired patients: Available clinical data suggest that dosage reductions may not be necessary in this patient population.

Hepatically impaired patients: The clearance of granisetron hydrochloride is reduced by half in patients with hepatic impairment. The dose response of granisetron hydrochloride in patients with hepatic impairment has not been determined.

Reconstitution

Diluted Solutions

Infusion Preparation

To prepare Granisetron Hydrochloride for i.v. infusion, aseptically transfer the appropriate amount of Granisetron Hydrochloride to the desired volume of any of the following solutions: 0.9% sodium chloride, 0.18% sodium chloride and 4% dextrose, 5% dextrose, Hartmann's solution, sodium lactate, mannitol. (See STORAGE AND STABILITY section).

OVERDOSAGE

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Granisetron hydrochloride is a selective antagonist of 5-hydroxytryptamine (5-HT_3) receptors. Following exposure to emetogenic cancer chemotherapy, mucosal enterochromaffin cells release serotonin which stimulates 5-HT_3 receptors located peripherally on vagal nerve terminals and centrally in the nucleus tractus solitarus. The antiemetic effect of granisetron appears to involve antagonism of the serotonin-induced stimulation of vagal afferent activity.

Radioligand binding studies have demonstrated that granisetron hydrochloride has negligible affinity for other 5-HT receptors or for dopamine D_2 receptor binding sites.

Pharmacodynamics

In healthy subjects, granisetron hydrochloride produced no consistent or clinically significant changes in pulse rate, blood pressure or ECG. There was no evidence of an effect on psychomotor performance at intravenous doses of up to 200 mcg/kg i.v. granisetron hydrochloride did not affect the plasma levels of prolactin or aldosterone at single intravenous doses of up to 300 mcg/kg or after repeat intravenous doses of 40 mcg/kg for 5.5 days.

Pharmacokinetics

Chemotherapy-Induced Nausea and Vomiting

In adult cancer patients undergoing chemotherapy and in healthy volunteers, infusion of a single 40 mcg/kg dose of granisetron hydrochloride produced the following mean pharmacokinetic data:

Table 2. Pharmacokinetic Parameters in Adult Cancer Patients Undergoing Chemotherapy and in Volunteers, Following a Single Intravenous 40 mcg/kg Dose of Granisetron Hydrochloride Injection

	Peak Plasma Concentration (ng/mL)	Terminal Phase Plasma Half-Life (h)	AUC (ng·h/mL)	Total Clearance (L/h)
Cancer Patients (N=14)				
Mean	63.8*	8.95*	167*	25.8*
Range	18.0 to 176	0.90 to 31.1	26.0 to 294	8.92 to 95.2
Young Adult Volunteers 21 to 42 years (N=20)				
Mean	64.3†	4.91†	89.7†	51.8†
Range	11.2 to 182	0.88 to 15.2	15.6 to 201	11.3 to 176
Elderly Volunteers 65 to 81 years (N=20)				
Mean	57.0†	7.69†	115†	27.1†
Range	14.6 to 153	2.65 to 17.7	37.7 to 240	10.9 to 58.4

* 5 minute infusion †3 minute infusion

Distribution: Granisetron hydrochloride is extensively distributed between plasma and red blood cells with a mean volume of distribution of approximately 3 L/kg. Plasma protein binding is approximately 65%.

Metabolism: The clearance of granisetron occurs predominantly through hepatic metabolism. Biotransformation pathways involve N-demethylation and aromatic ring oxidation followed by conjugation.

Excretion: In normal volunteers, the urinary excretion of unchanged granisetron hydrochloride averages 12% of the administered dose over a period of 48 hours, while the remainder of the dose is excreted as metabolites, 47% in the urine and 34% in the feces. The metabolism of granisetron involves N-demethylation and aromatic ring oxidation followed by conjugation.

Special Populations and Conditions

Pediatrics: The safety and efficacy of granisetron hydrochloride has not been adequately studied in children or adolescents under 18 years of age.

Geriatrics: In geriatric (mean age 71 years) subjects after single intravenous doses of 40 mcg/kg, pharmacokinetic parameters were within the range found for young subjects (mean age 29 years). Although the elimination half-life was prolonged and the total plasma clearance reduced in the geriatric relative to the young subject group, no significant differences were determined between the two groups with regard to maximum plasma concentration or area under the plasma concentration time curve values (see Table 2).

Gender/Race: There were too few male and Black patients to adequately assess differences in effect in either population.

Hepatic Insufficiency: A pharmacokinetic study in patients with hepatic impairment due to neoplastic liver involvement showed that total clearance was approximately halved and mean area under the plasma concentration time curve (AUC) values were approximately doubled compared to patients without hepatic impairment.

Renal Insufficiency: Although renal clearance was decreased in subjects with severe renal impairment (N=11) relative to normal volunteers (N=12), total plasma clearance was numerically higher in this renally impaired group (43 L/h) than in the normal volunteers (32 L/h). Mean area under the plasma concentration time curve values were similar for the two subject groups.

Cancer Patients: Following intravenous administration, mean terminal elimination half-life values are approximately twice as long in cancer patients as they are in healthy adult volunteers, while clearance values are decreased by approximately 50% (see Table 2).

STORAGE AND STABILITY

Vials should be stored at room temperature 15 - 30°C (59 - 86°F). Avoid freezing. Protect from light. Once the vial is penetrated, its contents should be used within 28 days. Discard unused portion.

Granisetron Hydrochloride has been shown to be stable for at least 24 hours in the following solutions: 0.9% sodium chloride, 0.18% sodium chloride and 4% dextrose, 5% dextrose, Hartmann's solution, sodium lactate, mannitol, when stored at ambient temperature in normal indoor illumination (natural daylight supplemented by fluorescent light). As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Appropriate precautions should be taken to maintain the sterility of the infusion solution once prepared.

Pharmaceutical Precautions

As a general precaution, Granisetron Hydrochloride should not be mixed in solution with other drugs.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

Granisetron Hydrochloride Injection is available as a sterile injectable solution.

Composition

Each 1 mL, 3 mL and 4 mL Multi-Dose vial contains 1 mg/mL granisetron as hydrochloride, 1.0% benzyl alcohol (as preservative), citric acid (monohydrate), sodium chloride, sodium citrate (dihydrate) and water for injection.

Packaging

Granisetron Hydrochloride is supplied in clear glass, multi-use vials of 1 mL, 3 mL or 4 mL, packaged in boxes of 1 vial. Each vial contains 1 mg/mL granisetron as hydrochloride.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

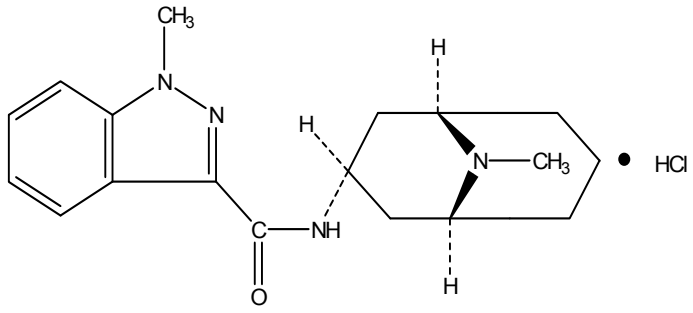
Proper Name: Granisetron Hydrochloride

Chemical Name: 1-Methyl-*N*-[(1*R*,3*r*,5*S*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1*H*-indazole-3-carboxamide hydrochloride

Molecular Formulae: $C_{18}H_{24}N_4O \cdot HCl$

Molecular Weight: 348.88

Structural formula:



Description: Granisetron hydrochloride is a white to off-white powder.

Solubility: Granisetron hydrochloride is freely soluble in water, sparingly soluble in methylene chloride and slightly soluble in methanol.

Polymorphism: All analytical methods used to test granisetron hydrochloride indicated that batches were all of the same crystal form and there were no additional polymorphs.

pH: The pH of a 1% aqueous solution is in the range of 4.0 - 6.5 (10 mg/mL in water).

Melting Point: The melting point of granisetron hydrochloride is approximately 292°C (decomposes when liquidation occurs).

CLINICAL TRIALS

Chemotherapy-Induced Nausea and Vomiting:

Granisetron hydrochloride injection has been shown to prevent nausea and vomiting associated with single-day and repeat-cycle cancer chemotherapy.

Single-Day 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 3).

Table 3. Prevention of Chemotherapy-Induced Nausea and Vomiting-Single-Day Cisplatin Therapy*

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

* Cisplatin administration began within 10 minutes of granisetron hydrochloride infusion and continued for 1.5 to 3.0 hours. Mean cisplatin doses were 86 mg/m^2 in the group of patients treated with granisetron hydrochloride injection group and 80 mg/m^2 in the placebo group.

† No vomiting and no moderate or severe nausea.

Granisetron hydrochloride injection was 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 4.

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

Dose of Granisetron Hydrochloride Injection (mcg/kg)	5	10	20	40
Number of Patients	82	90	88	93
Complete Response‡‡ (%)	23	48*	48*	44*
No Vomiting (%)	32	54*	53*	48*
No Nausea %	22	46*	38*	38*

‡ Cisplatin administration began within 10 minutes of granisetron hydrochloride infusion and continued 2 hours (mean). Mean cisplatin dose was 82 mg/m^2.

‡‡ No vomiting and no rescue medication.

* $p<0.05$ vs 5 mcg/kg.

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.

Repeat Cycle Chemotherapy

Two single blind, active-controlled studies have been performed in which granisetron hydrochloride injection was administered to a total of 246 chemotherapy-naive patients with malignant disease receiving cytostatic therapy (≥15 mg/m^2/day cisplatin, ≥1.2 g/m^2/day ifosfamide, and ≥120 mg/m^2 /day etoposide) for 5 days. Granisetron hydrochloride injection was administered as a daily 40 mcg/kg i.v. dose 5 min. before the infusion of the cytostatic with up to two additional 40 mcg/kg i.v. doses permitted over each 24 hr period. In both studies, response rates (percentage of patients with no vomiting and no more than mild nausea in the 24 hour period following administration of granisetron hydrochloride injection) were observed to decline with repeated treatment, decreasing from 87-90% at day 1 to 70-71% at day 3, and 67-73% at day 5.

DETAILED PHARMACOLOGY

Radioligand binding studies have been performed on rat and guinea pig brain membrane preparations. Granisetron appears to possess a high specificity for the 5-HT$_3$ receptor, while exhibiting negligible affinity for other 5-HT receptor subtypes (5-HT$_1$, 5-HT$_2$, 5-HT$_{1A}$, 5-HT$_{1B/c}$, 5-HT$_1$c) or α_1, α_2, or β-adrenoreceptors; dopamine-D$_2$, histamine-H$_1$, benzodiazepine, picrotoxin, or opioid binding sites.

The antagonistic effects of granisetron have been demonstrated in three models of 5-HT$_3$ receptor dependent activities. 1) transient bradycardia (the Von Bezold-Jarisch reflex) following the intravenous injection of 5-HT into anesthetized rats (IC_{50} = 0.7 mcg/kg), 2) 5-HT-induced contractions of the guinea pig isolated ileum (pA_2 = 8.1), and 3) tachycardia following 5-HT injection into the carotid arteries of the rabbit isolated heart (pA_2 = 10.7).

Two metabolites of granisetron (7-hydroxy metabolite and desmethyl metabolite) antagonized the Von Bezold-Jarisch reflex in anesthetized rats with potencies similar to that for the parent compound. However, the low plasma concentrations of these metabolites relative to the parent compound suggest that they are not likely to play a significant role following administration of granisetron.

Granisetron has proved efficacious both for the prophylaxis and treatment of emesis induced in the ferret by cisplatin, doxorubicin + cyclophosphamide, or X-irradiation. Maximal antiemetic efficacy in ferrets appeared to be achieved at a dose of 0.5 mg/kg i.v. administered 15 min. before chemotherapy or radiation therapy. Furthermore, when a 0.5 mg/kg i.v. dose of granisetron was administered during emetic episodes occurring 90 min. after cisplatin treatment,

cessation of emesis was observed within 5 to 30 sec. of injection.

Granisetron was however, ineffective as an antiemetic in a canine model of apomorphine-evoked emesis and a ferret model of morphine-induced emesis suggesting that dopamine D_2 and opioid receptor antagonism are not components of its mechanism of action.

Other than for some inhibition of locomotor activity in mice at 10 mcg/kg s.c. and in rats at 1 to 5 mg/kg s.c., granisetron did not exert central nervous system effects in the models studied. At cumulative doses up to 4.3 mg/kg i.v. administered over 2 hrs, granisetron had no effect on basal blood pressure or heart rate in conscious male rats. In the anaesthetized dog, however, granisetron was demonstrated to decrease arterial blood pressure, heart rate, and myocardial contractility in a dose-dependent manner over a 1 to 3 mg/kg dose range.

Gastrointestinal: Granisetron (0.1-1.0 mg/kg s.c.) was associated with reduced fecal pellet output in conscious mice, suggesting a constipating effect.

Reproductive: Granisetron inhibited 5-HT induced contractions of the non-pregnant rat uterus *in vitro* with an IC_{50} of 5.9 mcM.

Preclinical Pharmacokinetics

Pharmacokinetics and ADME of granisetron have been extensively studied in rat and dog, the main species used in the non-clinical toxicology studies. Information has also been obtained on the mouse (used for carcinogenicity assessment), rabbit (teratology assessment) and ferret (efficacy pharmacology).

In rat and dog after intravenous dosing, granisetron freely diffused between plasma and red cells. Plasma protein binding in rats and dogs was moderate, 57% and 45%, respectively. A volume of distribution equivalent to approximately 3 L/kg in both species reflected the extensive tissue uptake expected of a lipophilic amine. In the rat, low excretion of granisetron in urine (approximately 2% dose) and a total plasma clearance (3.7 L/h/kg) similar to hepatic blood flow classified granisetron as a highly extracted drug whose clearance was flow-rate limited. In the dog, the plasma clearance value (2.6 L/h/kg) and the low urinary excretion (2-4% dose) classified granisetron extraction as medium to high in this species. In both species, relatively short granisetron plasma half-lives were observed (approximately 0.7 hours) and linear kinetics were indicated by the proportionate increases of granisetron plasma AUC with dose. As expected, no accumulation was observed on repeated daily dosing.

Complete absorption of ^{14}C-granisetron from the gastrointestinal tract in rats, dogs, mice and rabbits was observed. However, oral bioavailability was severely reduced by the large first-pass effect resulting from the high liver extraction. Thus in rats, granisetron bioavailability was estimated at 0.2% of the dose after an oral dose of 5 mg/kg, whilst in dogs oral bioavailability

was higher (about 17% at 0.25 and 1.5 mg/kg p.o.) reflecting lower liver extraction. In both species, bioavailability increased at the high dose levels used in toxicology studies (rat: about 10% bioavailability at 100 mg/kg p.o.; dogs: about 80% at 10 mg/kg p.o.), as the increased drug input partially saturated the first-pass effect.

Granisetron-related material (radioactivity) was rapidly and widely distributed to tissues after intravenous or oral doses of ^{14}C-granisetron to rats. Whole body autoradiography and direct measurement revealed relatively high concentrations in excretory organs, liver and kidney, and low concentrations in blood and brain tissue. The time-course of elimination from tissues was similar to that from blood. The radioactivity was readily eliminated, such that only 1% remained in the tissues at 24 hours, though trace amounts were eliminated more slowly. Like many amine drugs, small amounts were taken up by melanin-containing tissues in pigmented animals and slowly released. On daily repeated intravenous dosing, minimal accumulation of radioactivity was observed in blood and tissues.

Granisetron was extensively metabolised, resulting in low excretion of unchanged drug in urine and feces. Metabolites found in mice, rats, rabbits, dogs and ferrets revealed that similar metabolic processes (oxidation at the N-methyl groups, oxidation in the benzenoid ring followed by sulphate and glucuronide conjugation, and a combination of these) were used in all species. However, quantitative differences between species were observed. Notably, 5-hydroxylation was higher than 7-hydroxylation in rats, mice and rabbits, whilst the converse was true for dogs and ferrets. Excretion of granisetron itself was low (no more than 13%) in all species studied. Granisetron excretion in feces accounted for less than 3% of the dose. Granisetron metabolites were readily excreted in both urine and feces of mice, rats, rabbits, dogs and ferrets. On administering ^{14}C-granisetron, urinary excretion of radioactivity in rats and dogs amounted to approximately 40% of the dose, irrespective of dose route, and the remainder was excreted in feces. In mice and rabbits, the urinary route accounted for about 60% dose, and in ferrets about 20% dose. The majority of urinary excretion occurred in the first 24 hours after dosing.

TOXICOLOGY

Acute Toxicity

The acute toxicity of granisetron is due primarily to CNS stimulation. LD_{50} values by the intravenous route are within the range of 14 to 25 mg/kg in rats and mice.

The intravenous LD_{50} for granisetron hydrochloride in mice is 17 mg/kg in males and 25 mg/kg in females. In rats it is 14 mg/kg in males and 16 mg/kg in females. The oral LD_{50} is 350 mg/kg in both male and female mice. It is 350 mg/kg in male rats and 1100 mg/kg in female rats.

Longterm Toxicity

Subacute Toxicity Studies

The subacute toxicity of granisetron was studied in the rat and dog; both species are suitable for the safety evaluation of granisetron hydrochloride on pharmacokinetic and metabolic grounds. In intravenous studies of up to 3 months duration in the rat, signs of acute CNS stimulation were dose limiting at 9 mg/kg/day. Histopathological examination revealed an increase in the fat content of the liver in the majority of females at 6 mg/kg/day after 13 weeks of treatment but not following a further 4 weeks off-dose. In the dog, intravenous studies of up to 3 months duration resulted in convulsions at near lethal doses (3 mg/kg/day). Increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were seen in some animals at 3 mg/kg/day but there were no histopathological findings to indicate target organ toxicity at this level. Following treatment for 3 months, the intravenous no-toxic-effect level in both species was 0.5 mg/kg/day, representing a factor of approximately 3 over the maximum anticipated daily clinical dose of granisetron hydrochloride.

Chronic Toxicity Studies

Granisetron was administered in oral repeat-dose studies of up to 12 months duration in the rat and dog.

In the 6 and 12 month rat studies, there were changes in plasma enzymes associated with liver function, however, none of these changes was evident in sub-groups of high dose animals maintained for an off-dose period after the treatment. Dose-related increases in liver weights were also seen in rats given granisetron for up to 52 weeks, in the diet; such increases occurred in males dosed at 25 mg/kg/day and above.

Morphometric analysis has confirmed that there was an increased number of hepatocytes per unit area at the high dose, indicating that the increased liver weights were associated with hepatocyte hyperplasia. There was no evidence of hyperplasia at a dose of 5 mg/kg/day. Although there were increased incidences of rats with foci or areas of acidophilic and/or basophilic hepatocyte alteration in the intermediate and high dose groups, precise morphometric quantification of the amount of liver occupied by foci demonstrated that increases compared with the controls were confined to the high dose. These results clearly define 5 mg/kg/day to be a no-effect dose, at which the drug does not cause the production of liver foci or induce hyperplasia. The morphometric analysis also showed that, at the high dose, the amount of liver occupied by foci regressed after cessation of treatment.

In the 6 month dog study, there was a trend toward increased alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) at the high dose of 10 mg/kg/day, although histopathological changes were not observed. Physical signs at the high dose during the initial stages of treatment consisted of prominence of the nictating membrane, black or dark discoloured feces and, in males, an increased incidence of loose feces. Emesis and isolated clonic convulsions were also noted. One high dose male died on Day 181 having shown no previous signs of ill health; the

cause of death could not be established. There were no toxic effects at the mid-dose of 1.5 mg/kg/day.

In the 12 month dog study, the high dose (5 mg/kg/day) produced no CNS effects and there were no changes in plasma enzymes indicative of altered hepatic function or treatment related histopathological findings at this dose.

Carcinogenicity Studies

In a 24-month carcinogenicity study, mice were treated orally with granisetron 1, 5 or 50 mg/kg/day. There was a statistically significant increase in the incidence of hepatocellular carcinomas in males and hepatocellular adenomas in females dosed with 50 mg/kg/day (5,000 times the recommended human dose given intravenously). No increase in liver tumours was observed in mice at a dose of 5 mg/kg/day (500 times the recommended human dose given intravenously).

In a 24-month carcinogenicity study, rats were treated orally with granisetron 1, 5 or 50 mg/kg/day. Owing to manifestations of toxicity, the 50 mg/kg dose was reduced to 25 mg/kg/day (2,500 times the recommended human dose given intravenously) from week 59 of treatment onwards. There was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in males dosed with 5 mg/kg/day (500 times the recommended human dose given intravenously) and above, and in females dosed with 50 mg/kg/day (5,000 times the recommended human dose given intravenously). No increase in liver tumors was observed in rats at a dose of 1 mg/kg/day (100 times the recommended human dose, given intravenously) in males and 5 mg/kg/day (500 times the recommended human dose given intravenously) in females.

Experimental evidence in rats shows that granisetron exhibits the characteristics of a promoter of liver tumors with a clear no-effect dose of 1 mg/kg (100 times the recommended human dose given intravenously). The probable mechanism for this effect is sustained liver cell hyperplasia. In a study in which rats were treated for 12 months with 100 mg/kg/day (10,000 times the recommended human dose given intravenously), the observed promoting effects were reversible upon cessation of treatment. Additionally, there was no adverse effect on the liver of dogs treated for 12 months with granisetron, 5 mg/kg/day (500 times the recommended human dose given intravenously).

Mutagenicity Studies

The effects of granisetron were investigated in a battery of seven tests for mutagenicity, including an investigation of DNA damage in rat hepatocytes. Granisetron did not cause gene mutation in Ames bacterial assays in *Salmonella* and *E. coli* or in a mouse lymphoma cell assay. No evidence of chromosomal damage was observed in human lymphocytes *in vitro* or in a mouse micronucleus test at doses of up to 1800 times the recommended human dose given intravenously. However, granisetron was associated with a significant increase in the number of

cells with polyploidy in an *in vitro* human lymphocyte chromosomal aberration test. There was no evidence of DNA damage and repair in assays of unscheduled DNA synthesis (UDS) in rat hepatocytes *in vitro* (or *in vivo* at doses of up to 35,000 times the recommended human dose given intravenously). There was an apparent increase in UDS in HeLa cells exposed to granisetron *in vitro* when DNA synthesis was measured by scintillation counting of incorporated radioactive thymidine. However, when this test was repeated using a more definitive autoradiographic methodology and microscopic examination of HeLa cells, the test was negative for UDS. It is likely that the apparent UDS in the initial study was, in fact, a reflection of DNA synthesis in cells undergoing normal division.

Reproduction

In a reproduction and fertility study in rats, granisetron at subcutaneous doses up to 6 mg/kg/day (600 times the recommended human dose given intravenously) had no effect on male or female fertility.

At dose levels which produced maternal toxicity, intravenous granisetron [up to 9 mg/kg/day (900 times the recommended human dose given intravenously) in rats, and up to 3 mg/kg/day (300 times the recommended human dose given intravenously) in rabbits] had no adverse effect on the course and outcome of pregnancy. A similar lack of effect was apparent in peri- and post-natal studies and general reproductive studies, in the rat.

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PART III: CONSUMER INFORMATION
PrGranisetron Hydrochloride Injection
Sterile

This leaflet is part III of a three-part "Product Monograph" published when Granisetron Hydrochloride was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Granisetron Hydrochloride. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Granisetron Hydrochloride is one of a group called antiemetics and it can only be obtained with a prescription from your doctor.

Granisetron Hydrochloride is intended to prevent nausea (feeling sick) and vomiting which may occur after you receive cancer chemotherapy.

What it does:
Cancer chemotherapies are thought to cause the release of serotonin, a natural substance in the body. Serotonin can cause you to feel sick and to vomit. Granisetron, the active ingredient in Granisetron Hydrochloride Injection, will stop the action of serotonin and help prevent you from feeling sick and vomiting.

When it should not be used:
Do not take this medicine if you are allergic to granisetron or any of its ingredients.

What the medicinal ingredient is:
Granisetron hydrochloride

What the nonmedicinal ingredients are:
Each injection contains the following inactive ingredients:
benzyl alcohol, citric acid (monohydrate), sodium chloride, sodium citrate (dihydrate) and water for injection.

What dosage forms it comes in:
Granisetron Hydrochloride is supplied in clear glass multi-use vials of 1 mL, 3 mL and 4 mL packaged in boxes of 1 vial. Each vial contains 1 mg/mL granisetron as hydrochloride.

WARNINGS AND PRECAUTIONS

BEFORE you use Granisetron Hydrochloride talk to your doctor or pharmacist if:

- you have any allergies to similar antiemetics such as dolasetron mesylate (Anzemet®) or ondansetron (Zofran®)
- you are pregnant, plan to become pregnant or are breastfeeding
- you have liver problems

As Granisetron Hydrochloride may cause drowsiness, you should avoid driving a car or operating hazardous machinery until you know it does not affect you.

PROPER USE OF THIS MEDICATION

This medicine is only for you, the person for whom the prescription was written. Do not give this medication to others.

Usual Adult Dose:
Granisetron Hydrochloride will be given to you by hospital staff before and/or after your therapy.

Overdosage:
There is no specific antidote, therefore symptomatic treatment should be initiated.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

If you experience an allergic reaction (e.g. shortness of breath, drop in blood pressure, skin lumps or hives), contact your doctor immediately. Do not take any more medicine unless instructed to do so by your doctor.

You may experience headaches, constipation, weakness, sleepiness, diarrhea or abdominal pain while taking Granisetron Hydrochloride. You may also experience pain, anemia or fever while on Granisetron Hydrochloride therapy. There is no need to stop the medicine but you should tell your doctor about these symptoms.

This is not a complete list of side effects. For any unexpected effects while taking Granisetron Hydrochloride, contact your doctor or pharmacist.

HOW TO STORE IT

Granisetron Hydrochloride vials should be stored at room temperature 15° - 30°C (59° – 86°F). Avoid freezing. Protect from light. Once the vial is penetrated, its contents should be used within 28 days. Discard unused portion.

The expiry date of this medicine is printed on the label. Do not use the medicine after this date. Keep your medicine in a safe place out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS
To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

Toll-free telephone: 866-234-2345
Toll-free fax: 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

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