PRODUCT MONOGRAPH

[Pr]APO-GRANISETRON

Granisetron Hydrochloride Tablets, USP

1 mg granisetron (as granisetron hydrochloride)

Antiemetic/5-HT_3 receptor antagonist

APOTEX INC.
150 Signet Drive
Toronto, Ontario
M9L 1T9
Control No.: 194711

DATE OF PREPARATION:
June 30, 2016

Table of Contents

[Pr]APO-GRANISETRON
Granisetron Hydrochloride

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
oral	tablet / 1 mg	lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and colloidal silicon dioxide, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycol and titanium dioxide CONTAINS LACTOSE

INDICATIONS AND CLINICAL USES

Indications
APO-GRANISETRON (granisetron hydrochloride) is indicated for:

Adults

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

- The prevention of nausea and vomiting associated with radiation, including total body irradiation and fractionated abdominal radiation.

Geriatrics (>65 years of age)
Chemotherapy-induced and Radiation-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 under18 years of age and it is not indicated for use in this population (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

- APO-GRANISETRON (granisetron hydrochloride) is contraindicated in patients with a known hypersensitivity to the drug or to any component of its formulations. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

- The concomitant use of APO-GRANISETRON with apomorphine is contraindicated based on reports of profound hypotension and loss of consciousness when apomorphine was administered with another 5-HT3 antagonist.

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).

Cardiovascular

As for other 5-HT_3 antagonists, cases of ECG modifications including QT prolongation have been reported with granisetron hydrochloride. These ECG changes with granisetron hydrochloride were minor and generally not of clinical significance, specifically with no evidence of proarrhythmia. However, in patients with pre-existing arrhythmias or cardiac conduction disorders, this might lead to clinical consequences. Therefore, caution should be exercised in patients with cardiac co-morbidities, on cardio-toxic chemotherapy and/or with concomitant electrolyte abnormalities. See also DRUG INTERACTIONS and ADVERSE REACTIONS, Post-marketing Reports of Adverse Events.

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.

It is recommended that APO-GRANISETRON film-coated tablets are not taken by patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption.

Serotonin Syndrome/Neuroleptic Malignant Syndrome-like Events

Cases of life-threatening serotonin syndrome have been reported with 5-HT_3 receptor antagonist antiemetics, including granisetron hydrochloride, particularly when given in combination with other serotonergic and/or neuroleptic drugs. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and /or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). As this syndrome may result in potentially life-threatening conditions, treatment should be discontinued if such events occur and supportive symptomatic treatment should be initiated. If concomitant treatment of granisetron hydrochloride with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observations of the patient is advised, particularly during treatment initiation and dose increases (see DRUG INTERACTIONS).

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

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

Adverse Drug Reaction Overview

The most common adverse events reported by patients receiving 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.

As for other 5-HT_3 antagonists, cases of ECG modifications including QT prolongation have been reported with granisetron hydrochloride. These ECG changes with granisetron hydrochloride were minor and generally not of clinical significance, specifically with no evidence of proarrhythmia (see WARNINGS AND PRECAUTIONS, Cardiovascular, DRUG INTERACTIONS, and ADVERSE REACTIONS, Post-marketing Reports of Adverse Events).

Clinical Trial Adverse Drug 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.

Chemotherapy-induced Nausea and Vomiting

Oral granisetron hydrochloride was given either as a single dose or divided dose for 1, 7, or 14 days. Patients received cancer chemotherapy which consisted primarily of cisplatin or cyclophosphamide regimens. Adverse events were recorded over seven days when granisetron hydrochloride was given on a single day and up to 28 days when granisetron hydrochloride was administered for 7 or 14 days. 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 or oral 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 Oral Granisetron Hydrochloride (1.0 mg twice daily or 2.0 mg once daily), (n=1322)
Headache	22%
Asthenia	15%
Somnolence	2%
Diarrhea	8%
Constipation	17%
Abdominal Pain	6%

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.

Radiation-induced Nausea and Vomiting
In controlled clinical trials, the adverse events reported by patients receiving granisetron hydrochloride tablets and concurrent radiation were similar to those reported by patients receiving granisetron hydrochloride tablets prior to chemotherapy. The most frequently reported adverse events were diarrhea (25.6%), asthenia (22.0%) and constipation (15.5%). Headache (7.7%), however, was less prevalent in this patient population. Table 2 lists the adverse experiences (>5%) in patients who received granisetron hydrochloride tablets or placebo.

Table 2. Principal Adverse Events in Clinical Trials – RINV

	Percentage of Patients with Event Oral Granisetron Hydrochloride (1.0 mg twice daily), (n=134)	Percentage of Patients with Event Placebo (n=128)
Diarrhea	28%	34%
Asthenia	25%	20%
Constipation	19%	5%
Abdominal Pain	11%	9%
Nausea (after 20 radiation fractions)	11%	9%
Decreased appetite	10%	7%
Pain	8%	4%
Headache	5%	11%

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

Chemotherapy-induced Nausea and Vomiting
The safety profile of granisetron hydrochloride has been evaluated in 3269 patients receiving intravenous granisetron hydrochloride (2 to 160 mcg/kg) and 2,600 patients receiving oral granisetron hydrochloride (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 are defined as: those occurring in less than 1/100 but at least 1/1000 patients

Rare experiences are defined 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 general terms that are 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

Post-Marketing Reports of Adverse Events

The post-marketing safety experience in over 4 million patients is consistent with the clinical trial safety information.

Cases of cardiac arrest, ventricular fibrillation, ventricular tachycardia, ECG QT prolonged, sudden death and syncope were reported rarely in post-marketing experience. Some reports showed temporal association with granisetron, most of them also presenting confounding factors such as concomitant medications, medical history, and/or known risk factors. The relationship to granisetron cannot be established or excluded, either as an effect of the drug alone or in combination with other factors (see WARNINGS AND PRECAUTIONS, Cardiovascular, and DRUG INTERACTIONS).

As with other 5-HT_3 antagonists, cases of serotonin syndrome (including altered mental status, autonomic dysfunction and neuromuscular abnormalities) have been reported following the concomitant use of granisetron hydrochloride and other serotonergic drugs (refer to WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

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 four times daily.).

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

As for other 5-HT_3 antagonists, cases of ECG modifications including QT prolongation have been reported with granisetron hydrochloride. These ECG changes with granisetron hydrochloride were minor and generally not of clinical significance, specifically with no evidence of proarrhythmia. However, in patients concurrently treated with drugs known to prolong QT interval and/or are arrhythmogenic, this may lead to clinical consequences.

Serotonin Syndrome
As with other serotonergic agents, serotonin syndrome, a potentially life-threatening condition, may occur with 5-HT_3 receptor antagonist antiemetic treatment, particularly with concomitant use of other agents that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, SNRIs, lithium, sibutramine, fentanyl and its analogues, dextromethorphan, tramadol, tapentadol, meperidine, methadone and pentazocine or St. John's Wort [Hypericum perforatum], and with drugs which impair metabolism of serotonin (such as MAOIs, including linezolid [an antibiotic which is a reversible non-selective MAOI], and methylene blue; See WARNINGS AND PRECAUTIONS).

DOSAGE AND ADMINISTRATION

Recommended Dose, Dosage Adjustment and Administration

Emetogenic Chemotherapy

Adults: The recommended dosage of oral granisetron hydrochloride is 2 mg on the day of chemotherapy. This may be administered either as a single dose (2 x 1 mg) one hour before chemotherapy or as a divided dose of 1 mg one hour before chemotherapy followed by a second 1 mg dose 12 hours post-chemotherapy. The need for additional doses beyond 24 hours post-chemotherapy has not been investigated.

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.

Radiation (either Total Irradiation or Fractionated Abdominal Radiation)
Adults: The recommended adult dosage of oral granisetron hydrochloride is 2 mg once daily. 2 x 1 mg tablets are taken one hour before radiation.

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.

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 both the intravenous and oral formulations. Overdosage of up to 38.5 mg of granisetron hydrochloride injection has been reported without symptoms or with the occurrence of a slight headache.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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.

Following single and multiple oral doses, granisetron hydrochloride slowed colonic transit in normal volunteers.

Pharmacokinetics

Chemotherapy-Induced Nausea and Vomiting

Injection:

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 3. 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			

Oral:
In healthy volunteers and adult cancer patients undergoing chemotherapy, administration of oral granisetron hydrochloride produced the following mean pharmacokinetic data (Table 4):

Table 4. Pharmacokinetic Parameters (Mean [range]) In Adult Cancer Patients Undergoing Chemotherapy and in Volunteers Following Oral Granisetron Hydrochloride.

	Peak Plasma Concentation (ng.mL)	Terminal Plasma Half-Life (h)	Area under Curve (ng·h/mL)	Total Clearance (L/h)
Cancer Patients 1.0 mg, twice daily ., 7 days (n=24)	8.19 [1.97 to 18.4]	N.D.*	54.2 [10.2 to 126]	34.1 [7.94 to 98.0]
Volunteers single dose (n=25)				
1.0 mg	4.10 [0.58 to 7.37]	8.74 [2.40 to 19.9]	43.7 [2.85 to 142]	53.3 [7.04 to 351]
2.5 mg	9.44 [1.68 to 19.5]	7.24 [2.54 to 17.0]	105 [7.75 to 319]	67.2 [7.84 to 323]

* Not determined after oral administration

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 yrs) subjects after single intravenous doses of 40 mcg/kg, pharmacokinetic parameters were within the range found for young subjects (mean age 29 yrs). 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 3).

Gender/Race: There were too few male and Black patients to adequately assess differences in effect in either population (see CLINICAL TRIALS section).

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 3). Available data do not allow a formal comparison of elimination half-life or clearance between volunteers and cancer patients receiving oral granisetron hydrochloride.

STORAGE AND STABILITY

Store tablets at room temperature 15°C -30°C (59°F -86°F).

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-GRANISETRON Tablets 1 mg: Each white to off-white, triangular biconvex film-coated tablet, engraved "GR" over "1" on one side, contains 1 mg of granisetron as granisetron hydrochloride. Available in bottles of 20, 1000 and in unit dose blister packs of 10.

In addition to granisetron hydrochloride, each film-coated tablet contains the non-medicinal ingredients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and colloidal silicon dioxide, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycol and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Granisetron Hydrochloride

Chemical Name:

1) 1*H*-Indazole-3-carboxamide,1-methyl-*N*-(-9-methyl-9-azabicyclo[3,3,1]non-3-yl)-, monohydrochloride, *endo*-;

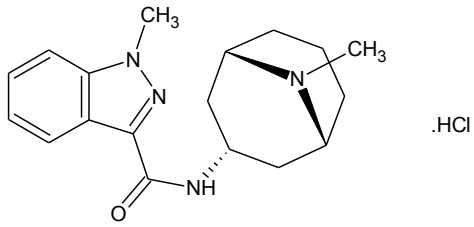
2) 1-Methyl-N-(9-methyl-endo-9-azabicyclo[3,3,1]non-3-yl)-1*H*-indazole-3-carboxamide monohydrochloride

3) 1-Methyl-N-(-endo-9-methyl-9-azabicyclo[3,3,1]non-3-yl)-1H-indazole-3-carboxamide hydrochloride

Molecular formula and molecular weight:

Granisetron: $C_{18}H_{24}N_4O$, 312.4
Granisetron Hydrochloride: $C_{18}H_{24}N_4O \cdot HCl$, 348.9

Structural Formula:



Physicochemical properties: White or almost white powder. Granisetron HCl is a crystalline material as evidenced by its powder x-ray pattern. Comprehensive literature search did not reveal any publications on Granisetron polymorphism.

Solubility:

Solubility in common solvents:

Freely soluble in water, sparingly soluble in methylene chloride, slightly soluble in methanol.

Quantitative aqueous pH solubility profile at 37°C:

Solvent	Initial pH Value	Final pH Value	Solubility (mg/mL)
H_2O	5.5	5.9	> 25
0.01N HCl	2.1	1.9	> 25
0.1N HCl	1.2	1.4	> 25
SGF	1.2	1.5	> 25
pH2.5 Buffer	2.5	2.4	> 25
pH3.5 Buffer	3.5	3.3	> 25
pH4.5 Buffer	4.5	4.4	> 25
pH5.5 Buffer	5.5	5.3	> 25
pH6.0 Buffer	6.0	5.7	> 25
pH6.8 Buffer	6.8	6.6	> 25
pH7.8 Buffer	7.8	7.3	> 25

pH: 4.0 to 6.5 (1% aqueous solution) . Typical value is 5.3.

pKa: 10.50±0.40 (Calculated using ACD labs software, version 6.0)

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized, single-dose, double-blinded, 2-way crossover comparative bioavailability study, conducted under fasting conditions, was performed on 26 healthy male volunteers. The rate and extent of absorption of granisetron was measured and compared following a single oral dose of Kytril® tablets (Granisetron hydrochloride) or APO-GRANISETRON tablets. The results from measured data are summarized in the following table (Table 5).

Table 5. Comparative Bioavailability Data for Granisetron Hydrochloride Tablets under Fasting Conditions.

Summary Table of the Comparative Bioavailability Data Apo-Granisetron (A single 1 mg dose: 1 x 1 mg tablet) From Measured Data/Fasting Conditions Geometric Mean Arithmetic Mean (CV%)				
Parameter	Apo-Granisetron	Kytril® †	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUCt (pg•h/mL)	38134.7 48686.5 (55)	42145.0 51199.9 (53)	90.5	81.5 - 100.4
AUCinf (pg•h/mL)	44707.9 60008.1 (64)	49802.8 63825.6 (62)	89.8	80.5 - 100.1
Cmax (pg/mL)	3289.5 3716.6 (43)	3561.8 3897.6 (38)	92.4	85.4 - 99.9
Tmax[#] (h)	2.68 (52)	2.55 (52)		
Thalf[#] (h)	10.21 (42)	10.80 (40)		
# Arithmetic means (CV%). † Kytril® is manufactured by Roche Laboratories Inc., and was purchased in the USA.				

Other Studies

<u>Chemotherapy-Induced Nausea and Vomiting</u>:

Oral:
Oral granisetron hydrochloride prevents nausea and vomiting associated with emetogenic cancer therapy as shown by 24-hour efficacy data from three double-blind studies. The first trial compared oral doses of granisetron hydrochloride of 0.25 mg to 2.0 mg twice daily in 930 cancer

patients receiving, principally, cyclophosphamide, carboplatin, or cisplatin (20mg/m^2 to 50mg/m^2) as chemotherapeutic agents. Table 6 summarizes the results of this study. The 1.0 mg twice daily dose of oral granisetron hydrochloride was demonstrated to produce the highest therapeutic benefit.

Table 6. Prevention of Nausea and Vomiting 24 Hours Post-Chemotherapy[1] Percentages of Patients.

Efficacy Measures	Oral Dose of Granisetron Hydrochloride			
	0.25 mg twice daily (n=229), %	0.5 mg twice daily (n=235), %	1.0 mg twice daily (n=233), %	2.0 mg twice daily (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, and not withdrawn/discontinued during treatment period.
* Statistically significant ($p<0.01$) vs. 0.25 mg twice daily
+ Statistically significant ($p<0.01$) vs. 0.5 mg twice daily

A second double-blind randomized trial compared oral granisetron hydrochloride 1.0 mg, twice daily, oral granisetron hydrochloride plus dexamethasone, and metoclopramide plus dexamethasone in 357 patients receiving cisplatin (mean dose > 80 mg/m^2). The complete response rate for the regimen with granisetron hydrochloride plus dexamethasone was significantly better than for granisetron hydrochloride alone, or the regimen with metoclopramide plus dexamethasone. Table 7 summarizes the results of this study.

Table 7. Prevention of Nausea and Vomiting 24 Hours Post-High Dose Cisplatin Therapy (Percentage of Patients)

Efficacy Measures	Antiemetic Regimen		
	Oral Granisetron Hydrochloride 1.0 mg twice daily (n=119), %	Oral Granisetron Hydrochloride 1.0 mg twice daily plus Dexamethasone 12mg IV (n=117), %	Metoclopramide 7mg/kg IV plus Dexamethasone 12mg IV (n=121), %
Complete Response[1]	52	65*	52
No Vomiting	56	66	52
No Nausea	45	57	39

[1] No emetic episodes, no moderate or severe nausea, no rescue medication, and not withdrawn/discontinued during treatment period.
* Statistically significant ($p<0.05$) vs. oral granisetron hydrochloirde alone and vs. metoclopramide plus dexamethasone.

The third study compared once daily versus twice daily dosing regimens with 2 mg/day of oral granisetron in 700 patients. Approximately 50% of patients who received granisetron 2 mg daily administered either as a single dose (n = 344) or in divided doses (n = 356), were free of emetic episodes and nausea and did not require antiemetic rescue treatment during the 24-hour post-chemotherapy period.

The continued efficacy of granisetron tablets 2 mg once daily or 1 mg twice daily, administered on the day of chemotherapy only, has not been investigated beyond the 24 hour post-chemotherapy period.
It is not known whether additional doses confer efficacy beyond 24 hours.

No controlled study has been performed to compare the antiemetic efficacy of granisetron tablets and granisetron injection at the recommended therapeutic doses.

Radiation-Induced Nausea and Vomiting:

Oral:
Oral granisetron hydrochloride prevents nausea and vomiting associated with total body irradiation and fractionated abdominal radiation.

Total Body Irradiation:
In a double-blind randomized study, 18 patients receiving granisetron hydrochloride tablets, 2 mg daily, experienced significantly greater antiemetic protection for patients receiving total body irradiation 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 3 fractions on each of the first 3 days, and two fractions on the fourth day. Eight of the 18 patients received the full 11 fractions of total body irradiation. Granisetron hydrochloride tablets were given one hour before the first irradiation fraction of each day.

Twenty-two percent (22%) of patients treated with granisetron hydrochloride tablets for the entire 4 day dosing period did not experience vomiting or receive antiemetics, compared to 0% of patients in the historical negative control group (n=90) ($p<0.01$). Patients who received granisetron hydrochloride 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 granisetron hydrochloride tablets.

Fractionated Abdominal Radiation:
The efficacy of granisetron hydrochloride, 2 mg daily, was evaluated in a double-blind, placebo-controlled randomized trial of 260 patients. Granisetron hydrochloride 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.

Patients treated with granisetron hydrochloride tablets (n=134) had a significantly longer time to the first episode of vomiting (35 vs. 9 days, $p<0.001$) relative to those patients who received placebo (n=126). Overall, 58% of the patients who received granisetron hydrochloride did not vomit compared to 42% of patients who received placebo ($p=0.0047$).

Patients treated with granisetron hydrochloride tablets also had a significantly longer time to the first episode of nausea (11 vs. 1 day, $p<0.001$), relative to the placebo treated patients. Overall, 31% of the patients who received granisetron hydrochloride tablets and 17% of patients who received placebo were nausea-free ($p=0.0042$).

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_{1C}) or ∞_1, ∞_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 faecal 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 the 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.

REFERENCES

1) Andrews PLR, Rapeport WG, Sanger GJ. Neuropharmacology of emesis induced by anti-cancer chemotherapy.TiPS 1988; 9: 334-341.

2) Andrews PLR, Hawthorn JA. The neurophysiology of vomiting. Balliere's Clin Gastroenterol 1988;2(1):141-168.

3) Bermudez J, Boyle EA, Miner WD, *et al*. The anti-emetic potential of the 5-hydroxytryptamine3 receptor antagonist BRL 43694. Br J Cancer 1988;58:644-650.

4) Hawthorn J, Ostler KJ, *et al*. The role of the abdominal visceral innervation and 5-hydroxytryptamine Mreceptors in vomiting induced by the cytotoxic drugs cyclophosphamide and cisplatin in the ferret. Q J Exp Physiol 1988;73:7-21.

5) Goddard PM, Jones M, Pollard LA. The 5-HT3 antagonist, BRL 43694, does not compromise the efficacy of cisplatin in tumor-bearing mice. Cancer Chemother Pharmacol 1990;25(5):377-9.

6) Pratt GD, Bowery NG, Kilpatrick GT *et al*. Consensus meeting agrees distribution of 5-HT3 receptors in mammalian hindbrain. TiPS 1990;11:135-7.

7) Cupissol D. The efficacy of granisetron as a prophylactic antiemetic and intervention agent in high-dose cisplatin-induced emesis. Eur J Cancer 1990;26 (Suppl. 1):S23-S27.

8) Granisetron study group. The antiemetic efficacy and safety of granisetron compared with metoclopramide plus dexamethasone in patients receiving fractionated chemotherapy over 5 days. J Cancer Res Clin Oncol 1993;119:555-9.

9) Bremer K. A single-blind study of the efficacy and safety of intravenous granisetron compared with alizapride plus dexamethasone in the prophylaxis and control of emesis in patients receiving 5-day cytostatic therapy. Eur J Cancer 1992;28A (Suppl. 6/7):1018-1022.

10) Carmichael J *et al*. I.V. granisetron versus i.v.. granisetron plus i.v. dexamethasone in the prophylaxis of emesis induced by cytotoxic chemotherapy. Abstract presented at ECCO 7, Jerusalem 1993.

11) Hacking A. Oral granisetron - simple and effective: A preliminary report. Eur J Cancer 1992;28A(1):S28-S32.

12) Bleiberg HH *et al.* Antiemetic treatment with oral granisetron in patients receiving moderately emetogenic chemotherapy: A dose-ranging study. Clin Ther 1995;17(1):38-50.

13) Heron JF *et al.* Oral granisetron alone and in combination with dexamethasone: A double-blind randomized comparison against high-dose metoclopramide plus dexamethasone in prevention of cisplatin-induced emesis. Ann Oncol 1994;5(7):579-584.

14) Cupissol D *et al.* Evaluation of the bioequivalence of tablet and capsule formulations of granisetron in patients undergoing cytotoxic chemo-therapy for malignant disease. J Pharm Sci 1993;82(12):1281-4.

15) Gralla, RJ. *et al.* Single-dose oral granisetron has equivalent antiemetic efficacy intravenous ondansetron for highly emetogenic cisplatin-based chemotherapy. J Clin Oncol 1998;Vol 16(4):1568-1573.

16) Perez, EA *et al*. Comparison of single-dose oral granisetron versus intravenous ondansetron in the prevention of nausea and vomiting induced by moderately emetogenic chemotherapy: A multicenter, double-blind, randomized parallel study. J Clin Oncol 1998;Vol.16(2):754-760.

17) Product Monograph. Kytril® (granisetron hydrochloride), Tablets, Antiemetic (5-HT3 receptor antagonist); Hoffman-La Roche Limited, Mississauga, Ontario, Canada. Date of Revision: June 6, 2014, Control Number: 172914.

PART III: CONSUMER INFORMATION

[Pr]APO-GRANISETRON
Granisetron Hydrochloride Tablets, USP

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

ABOUT THIS MEDICATION

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

APO-GRANISETRON is intended to prevent nausea (feeling sick) and vomiting which may occur after you receive cancer chemotherapy or radiotherapy.

What it does:
Cancer chemotherapies and radiation therapies 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 APO-GRANISETRON tablets, 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 the ingredients APO-GRANISETRON contains.
- If you are taking apomorphine.

What the medicinal ingredient is:
Granisetron hydrochloride

What the non-medicinal ingredients are:
Each tablet contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and colloidal silicon dioxide (hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycol and titanium dioxide).

What dosage forms it comes in:
APO-GRANISETRON tablets are supplied in one strength:
1 mg tablets.

WARNINGS AND PRECAUTIONS

BEFORE you use APO-GRANISETRON 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
- you have a history of heart problems.
- You have galactose intolerance, lactase deficiency (lactose intolerance) or glucose-galactose absorption issues, since APO-GRANISETRON contains lactose, which is a type of sugar.
- you have been told by a doctor that you have a blockage of your gut or if you have severe constipation, pain or swelling in your stomach.
- you are taking other medications, including drugs you can buy without a prescription and herbal products.

Serotonin Syndrome is a rare but potentially life-threatening reaction that may occur if you take APO-GRANISETRON with certain other medications. It may cause serious changes in how your brain, muscles, and digestive system work. Be sure to tell your healthcare processional all the medicines you are taking.

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

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. To avoid potentially life-threatening reactions, tell your healthcare professional about **ALL** the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

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:
Follow your doctor's instructions about how often you should take your medicine and how many tablets you should take. This information is also on the label of the container of your medicine and if not, of if you have any questions, you should consult your doctor or pharmacist.

Do not take more tablets or take your tablets more often than your doctor prescribes.

Overdose:

In the event that you accidentally take more tablets than your doctor prescribes, immediately contact your doctor, hospital emergency department, or the nearest Poison Control Centre, even if you do not feel ill.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take a tablet at the time it should be taken, take the tablet as soon as you remember it was missed.

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 APO-GRANISETRON. There is no need to stop the medicine but you should tell your doctor about these symptoms.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Rare	**Allergic reaction –** symptoms include swelling of the mouth, throat, difficulty in breathing, rash, hives, increased heart rate			✓
	Disturbance in heart rhythm - dizziness, palpitations (fast, pounding or irregular heart beat), chest pain, fainting			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
	Serotonin Syndrome - symptoms that may be observed when APO-GRANISETRON is taken with certain other medications include: • Fever, sweating, shivering, diarrhea, nausea, vomiting • Muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination • Fast heartbeat, changes in blood pressure • Confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma			✓

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

HOW TO STORE IT

Store at room temperature 15°C - 30°C (59°F -86°F).

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.

IMPORTANT: PLEASE READ

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting DISpedia, Apotex's Drug Information Service at:

1-800-667-4708

This leaflet can also be found at: http://www.apotex.ca/products. This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

Last Prepared: June 30, 2016