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Infanrix—Cont.

suitable germicide. After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel. Do not administer this product subcutaneously.

Primary Immunization

The primary immunization course for children less than 7 years of age is three doses of 0.5 mL, given intramuscularly, at 4- to 8-week intervals (preferably 8 weeks). The customary age for the first dose is 2 months of age, but it may be given starting at 6 weeks of age and up to the seventh birthday. It is recommended that *Infanrix* be given for all three doses since no interchangeability data on acellular DTP vaccines exist for the primary series. *Infanrix* may be used to complete the primary series in infants who have received one or two doses of whole-cell DTP vaccine. However, the safety and efficacy of *Infanrix* in such infants have not been evaluated.

Booster Immunization

When *Infanrix* is given for the primary series, a fourth dose is recommended at 15 to 20 months of age. The interval between the third and fourth dose should be at least 6 months. At this time, data are insufficient to establish the frequency of adverse events following a fifth dose of *Infanrix* in children who have previously received four doses of *Infanrix*.

If a child has received whole-cell DTP vaccine for one or more doses, *Infanrix* may be given to complete the five-dose series. A fourth dose is recommended at 15 to 20 months of age. The interval between the third and fourth dose should be at least 6 months. Children 4 to 6 years of age (up to the seventh birthday) who received all four doses by the fourth birthday, including one or more doses of whole-cell DTP vaccine, should receive a single dose of *Infanrix* before entering kindergarten or elementary school. This dose is not needed if the fourth dose was given on or after the fourth birthday.

Additional Dosing Information

If any recommended dose of pertussis vaccine cannot be given, DT (For Pediatric Use) should be given as needed to complete the series.

Interruption of the recommended schedule with a delay between doses should not interfere with the final immunity achieved with *Infanrix*. There is no need to start the series over again, regardless of the time elapsed between doses.

The use of reduced volume (fractional doses) is not recommended. The effect of such practices on the frequency of serious adverse events and on protection against disease has not been determined.[17]

Preterm infants should be vaccinated according to their chronological age from birth.[17]

For persons 7 years of age or older, Tetanus and Diphtheria Toxoids (Td) for adult use should be given for routine booster immunization against tetanus and diphtheria.

Simultaneous Vaccine Administration

In clinical trials, *Infanrix* was routinely administered, at separate sites, concomitantly with one or more of the following vaccines: poliovirus vaccine live oral (OPV), hepatitis B vaccine, and *Haemophilus influenzae* type b vaccine (Hib) (see CLINICAL PHARMACOLOGY).

No data are available on the simultaneous administration of measles, mumps and rubella vaccine (MMR), varicella vaccine or inactivated polio virus (IPV) with *Infanrix*.

When concomitant administration of other vaccines is required, they should be given with different syringes and at different injection sites.

The ACIP encourages routine simultaneous administration of acellular DTP, OPV (or IPV), Hib, MMR and hepatitis B vaccine for children who are at the recommended age to receive these vaccines and for whom no specific contraindications exist at the time of the visit, unless, in the judgment of the provider, complete vaccination of the child will not be compromised by administering vaccines at different visits. Simultaneous administration is particularly important if the child might not return for subsequent vaccinations.[17]

STORAGE

Store *Infanrix* between 2°and 8°C (36°and 46°F). **Do not freeze.** Discard if the vaccine has been frozen. Do not use after expiration date shown on the label.

HOW SUPPLIED

Infanrix (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) is supplied as a turbid white suspension in vials containing a 0.5 mL single dose, in packages of 10 vials.

NDC 58160-840-11 (package of 10)

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Veterans Administration/Military/PHS—0.5 mL Single-Dose Vial, 10's, 6505-01-442-6262.
IN:L3

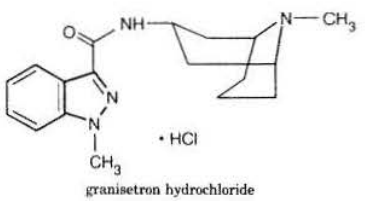
Shown in Product Identification Guide, page 337

KYTRIL® R

[*kī '-tril*]
granisetron hydrochloride
Injection

DESCRIPTION

Kytril (granisetron hydrochloride) Injection is an antinauseant and antiemetic agent. Chemically it is *endo*-N-(9-methyl-9-azabicyclo [3.3.1] non-3-yl)-1-methyl-1H-indazole-3-carboxamide hydrochloride with a molecular weight of 348.9 (312.4 free base). Its empirical formula is $C_{18}H_{24}N_4O{\cdot}HCl$ while its chemical structure is:



granisetron hydrochloride

Granisetron hydrochloride is a white to off-white solid that is readily soluble in water and normal saline at 20°C. *Kytril* Injection is a clear, colorless, sterile, nonpyrogenic, aqueous solution for intravenous administration.

Kytril is available in 1 mL single-dose and 4 mL multi-dose vials.

Single-Dose Vials: Each 1 mL of preservative-free aqueous solution contains 1.12 mg granisetron hydrochloride equivalent to granisetron, 1.0 mg and sodium chloride, 9.0 mg. The solution's pH ranges from 4.7 to 7.3.

Multi-Dose Vials: Each 1 mL contains 1.12 mg granisetron hydrochloride equivalent to granisetron, 1.0 mg; sodium chloride, 9 mg; citric acid, 2 mg; benzyl alcohol, 10 mg, as a preservative. The solution's pH ranges from 4.0 to 6.0.

CLINICAL PHARMACOLOGY

Granisetron is a selective 5-hydroxytryptamine$_3$ (5-HT_3) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT_1; 5-HT_{1A}; $5\text{-HT}_{1B/C}$; 5-HT_2; for $alpha_1$-, $alpha_2$- or beta-adrenoreceptors; for dopamine-D_2; or for histamine-H_1; benzodiazepine; picrotoxin, or opioid receptors.

Serotonin receptors of the 5-HT_3 type are located peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. During chemotherapy-induced vomiting, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT_3 receptors. This evokes vagal afferent discharge, inducing vomiting. Animal studies demonstrate that, in binding to 5-HT_3 receptors, granisetron blocks serotonin stimulation and subsequent vomiting after emetogenic stimuli such as cisplatin. In the ferret animal model, a single granisetron injection prevented vomiting due to high-dose cisplatin or arrested vomiting within 5 to 30 seconds.

In most human studies, granisetron has had little effect on blood pressure, heart rate or ECG. No evidence of an effect on plasma prolactin or aldosterone concentrations has been found in other studies.

Kytril Injection exhibited no effect on oro-cecal transit time in normal volunteers given a single intravenous infusion of 50 mcg/kg or 200 mcg/kg. Single and multiple oral doses slowed colonic transit in normal volunteers.

Pharmacokinetics

In adult cancer patients undergoing chemotherapy and in volunteers, infusion of a single 40 mcg/kg dose of *Kytril* Injection produced the following mean pharmacokinetic data: (See table 1 above)

There was high inter and intrasubject variability noted in these studies. No difference in mean AUC was found between males and females, although males had a higher C_{max} generally.

Granisetron metabolism involves N-demethylation and aromatic ring oxidation followed by conjugation. Animal studies suggest that some of the metabolites may also have 5-HT_3 receptor antagonist activity.

Clearance is predominantly by hepatic metabolism. In normal volunteers, approximately 12% of the administered dose is eliminated unchanged in the urine in 48 hours. The remainder of the dose is excreted as metabolites, 49% in the urine and 34% in the feces.

In vitro liver microsomal studies show that granisetron's major route of metabolism is inhibited by ketoconazole, suggestive of metabolism mediated by the cytochrome P-450 3A subfamily.

Plasma protein binding is approximately 65% and granisetron distributes freely between plasma and red blood cells.

Elderly: The ranges of the pharmacokinetic parameters in elderly volunteers (mean age 71 years), given a single 40 mcg/kg intravenous dose of *Kytril* Injection, were generally similar to those in younger healthy volunteers; mean values were lower for clearance and longer for half-life in the elderly (see Table 1).

Pediatric Patients: A pharmacokinetic study in pediatric cancer patients (2 to 16 years of age), given a single 40 mcg/kg intravenous dose of *Kytril* Injection, showed that volume of distribution and total clearance increased with age. No relationship with age was observed for peak plasma concentration or terminal phase plasma half-life. When volume of distribution and total clearance are adjusted for body weight, the pharmacokinetics of granisetron are similar in pediatric and adult cancer patients.

Renal Failure Patients: Total clearance of granisetron was not affected in patients with severe renal failure who received a single 40 mcg/kg intravenous dose of *Kytril* Injection.

Hepatically Impaired Patients: A pharmacokinetic study in patients with hepatic impairment due to neoplastic liver involvement showed that total clearance was approximately halved compared to patients without hepatic impairment. Given the wide variability in pharmacokinetic parameters noted in patients and the good tolerance of doses well above the recommended 10 mcg/kg dose, dosage adjustment in patients with possible hepatic functional impairment is not necessary.

CLINICAL TRIALS

Kytril Injection has been shown to prevent nausea and vomiting associated with single-day and repeat cycle cancer chemotherapy.

Single-Day Chemotherapy

Cisplatin-Based Chemotherapy: In a double-blind, placebo-controlled study in 28 cancer patients, *Kytril* Injection, administered as a single intravenous infusion of 40 mcg/kg, was significantly more effective than placebo in preventing nausea and vomiting induced by cisplatin chemotherapy. See Table 2.

Table 2. Prevention of Chemotherapy-Induced Nausea and Vomiting—Single-Day Cisplatin Therapy [1]

	Kytril Injection	Placebo	*P*-Value
Number of Patients	14	14	
Response Over 24 Hours			
Complete Response[2]	93%	7%	<0.001
No Vomiting	93%	14%	<0.001
No More Than Mild Nausea	93%	7%	<0.001

1. Cisplatin administration began within 10 minutes of *Kytril* Injection infusion and continued for 1.5 to 3.0 hours. Mean cisplatin dose was 86 mg/m^2 in the *Kytril* Injection group and 80 mg/m^2 in the placebo group.
2. No vomiting and no moderate or severe nausea.

Kytril Injection was also evaluated in a randomized dose response study of cancer patients receiving cisplatin >75 mg/m^2. Additional chemotherapeutic agents included: anthracyclines, carboplatin, cytostatic antibiotics, folic acid derivatives, methylhydrazine, nitrogen mustard analogs, podophyllotoxin derivatives, pyrimidine analogs and vinca alkaloids. *Kytril* Injection doses of 10 and 40 mcg/kg were superior to 2 mcg/kg in preventing cisplatin-induced nausea and vomiting, but 40 mcg/kg was not significantly superior to 10 mcg/kg. See Table 3.

(See table 3 above)

Kytril (granisetron hydrochloride) Injection was also 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.

(See table 4 above)

For both the low and high cisplatin strata, the 10, 20 and 40 mcg/kg doses were more effective than the 5 mcg/kg dose in preventing nausea and vomiting within 24 hours of chemotherapy administration. The 10 mcg/kg dose was at least as effective as the higher doses.

Table 1. Pharmacokinetic Parameters in Adult Cancer Patients Undergoing Chemotherapy and in Volunteers, Following a Single Intravenous 40 mcg/kg Dose of Kytril (granisetron hydrochloride) Injection

	Peak Plasma Concentration (ng/mL)	Terminal Phase Plasma Half-Life (h)	Total Clearance (L/h/kg)	Volume of Distribution (L/kg)
Cancer Patients				
Mean	63.8*	8.95*	0.38*	3.07*
Range	18.9 to 176	0.90 to 31.1	0.14 to 1.54	0.85 to 10.4
Volunteers				
21 to 42 years				
Mean	64.3†	4.91†	0.79†	3.04†
Range	11.2 to 182	0.88 to 15.2	0.20 to 2.56	1.68 to 6.13
65 to 81 years				
Mean	57.0†	7.69†	0.44†	3.97†
Range	14.6 to 153	2.65 to 17.7	0.17 to 1.06	1.75 to 7.01

* 5-minute infusion.
† 3-minute infusion.

Table 3. Prevention of Chemotherapy-Induced Nausea and Vomiting—Single-Day High-Dose Cisplatin Therapy [1]

	Kytril Injection (mcg/kg)			*P*-Value (vs. 2 mcg/kg)	
	2	10	40	10	40
Number of Patients	52	52	53		
Response Over 24 Hours					
Complete Response[2]	31%	62%	68%	<0.002	<0.001
No Vomiting	38%	65%	74%	<0.001	<0.001
No More Than Mild Nausea	58%	75%	79%	NS	0.007

1. Cisplatin administration began within 10 minutes of *Kytril* Injection infusion and continued for 2.6 hours (mean). Mean cisplatin doses were 96 to 99 mg/m^2.
2. No vomiting and no moderate or severe nausea.

Table 4. Prevention of Chemotherapy-Induced Nausea and Vomiting—Single-Day High-Dose and Low-Dose Cisplatin Therapy [1]

	Kytril Injection (mcg/kg)				*P*-Value (vs. 5 mcg/kg)		
	5	10	20	40	10	20	40
High-Dose Cisplatin							
Number of Patients	40	49	48	47			
Response Over 24 Hours							
Complete Response[2]	18%	41%	40%	47%	0.018	0.025	0.004
No Vomiting	28%	47%	44%	53%	NS	NS	0.016
No Nausea	15%	35%	38%	43%	0.036	0.019	0.005
Low-Dose Cisplatin							
Number of Patients	42	41	40	46			
Response Over 24 Hours							
Complete Response[2]	29%	59%	58%	41%	0.012	0.009	NS
No Vomiting	36%	63%	65%	43%	0.012	0.008	NS
No Nausea	29%	56%	38%	33%	0.012	NS	NS

1. Cisplatin administration began within 10 minutes of *Kytril* Injection infusion and continued for 2 hours (mean). Mean cisplatin doses were 64 and 98 mg/m^2 for low and high strata.
2. No vomiting and no use of rescue antiemetic.

Moderately Emetogenic Chemotherapy: *Kytril* Injection, 40 mcg/kg, was compared with the combination of chlorpromazine (50 to 200 mg/24 hours) and dexamethasone (12 mg) in patients treated with moderately emetogenic chemotherapy, including primarily carboplatin >300 mg/m^2, cisplatin 20 to 50 mg/m^2 and cyclophosphamide >600 mg/m^2. *Kytril* Injection was superior to the chlorpromazine regimen in preventing nausea and vomiting. See Table 5.

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

	Kytril Injection	Chlorpromazine [1]	*P*-Value
Number of Patients	133	133	
Response Over 24 Hours			
Complete Response[2]	68%	47%	<0.001
No Vomiting	73%	53%	<0.001
No More Than Mild Nausea	77%	59%	<0.001

1. Patients also received dexamethasone, 12 mg.
2. No vomiting and no moderate or severe nausea.

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

Repeat-Cycle Chemotherapy

In an uncontrolled trial, 512 cancer patients received *Kytril* Injection, 40 mcg/kg, prophylactically, for two cycles of chemotherapy, 224 patients received it for at least four cycles and 108 patients received it for at least six cycles.

Continued on next page

Information on the SmithKline Beecham Pharmaceuticals products appearing here is based on the labeling in effect on June 15, 2000. Further information on these and other products may be obtained from the Medical Department, SmithKline Beecham Pharmaceuticals, One Franklin Plaza, Philadelphia, PA 19101.

Kytril Injection—Cont.

Kytril Injection efficacy remained relatively constant over the first six repeat cycles, with complete response rates (no vomiting and no moderate or severe nausea in 24 hours) of 60% to 69%. No patients were studied for more than 15 cycles.

Pediatric Studies

A randomized double-blind study evaluated the 24-hour response of 80 pediatric cancer patients (age 2 to 16 years) to *Kytril* Injection 10, 20 or 40 mcg/kg. Patients were treated with cisplatin ≥60 mg/m², cytarabine ≥3 g/m², cyclophosphamide ≥1 g/m² or nitrogen mustard ≥6 mg/m². See Table 6.

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

	Kytril Injection Dose (mcg/kg)		
	10	20	40
Number of Patients	29	26	25
Median Number of Vomiting Episodes	2	3	1
Complete Response Over 24 Hours[1]	21%	31%	32%

1. No vomiting and no moderate or severe nausea.

A second pediatric study compared *Kytril* Injection 20 mcg/kg to chlorpromazine plus dexamethasone in 88 patients treated with ifosfamide ≥3 g/m²/day for two or three days. *Kytril* Injection was administered on each day of ifosfamide treatment. At 24 hours, 22% of *Kytril* Injection patients achieved complete response (no vomiting and no moderate or severe nausea in 24 hours) compared with 10% on the chlorpromazine regimen. The median number of vomiting episodes with *Kytril* Injection was 1.5; with chlorpromazine it was 7.0.

INDICATIONS AND USAGE

Kytril (granisetron hydrochloride) Injection is indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin.

CONTRAINDICATIONS

Kytril Injection is contraindicated in patients with known hypersensitivity to the drug or to any of its components.

PRECAUTIONS

Drug Interactions

Granisetron does not induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system. There have been no definitive drug-drug interaction studies to examine pharmacokinetic or pharmacodynamic interaction with other drugs, but in humans, *Kytril* Injection has been safely administered with drugs representing benzodiazepines, neuroleptics and anti-ulcer medications commonly prescribed with antiemetic treatments. *Kytril* Injection also does not appear to interact with emetogenic cancer chemotherapies. Because granisetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes, inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of granisetron.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month carcinogenicity study, rats were treated orally with granisetron 1, 5 or 50 mg/kg/day (6, 30 or 300 mg/m²/day). The 50 mg/kg/day dose was reduced to 25 mg/kg/day (150 mg/m²/day) during week 59 due to toxicity. For a 50 kg person of average height (1.46m² body surface area), these doses represent 16, 81 and 405 times the recommended clinical dose (0.37 mg/m², i.v.) on a body surface area basis. There was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in males treated with 5 mg/kg/day (30 mg/m²/day, 81 times the recommended human dose based on body surface area) and above, and in females treated with 25 mg/kg/day (150 mg/m²/day, 405 times the recommended human dose based on body surface area). No increase in liver tumors was observed at a dose of 1 mg/kg/day (6 mg/m²/day, 16 times the recommended human dose based on body surface area) in males and 5 mg/kg/day (30 mg/m²/day, 81 times the recommended human dose based on body surface area) in females. In a 12-month oral toxicity study, treatment with granisetron 100 mg/kg/day (600 mg/m²/day, 1622 times the recommended human dose based on body surface area) produced hepatocellular adenomas in male and female rats while no such tumors were found in the control rats. A 24-month mouse carcinogenicity study of granisetron did not show a statistically significant increase in tumor incidence, but the study was not conclusive.

Because of the tumor findings in rat studies, Kytril (granisetron hydrochloride) Injection should be prescribed only at the dose and for the indication recommended (see INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION).

Granisetron was not mutagenic in *in vitro* Ames test and mouse lymphoma cell forward mutation assay, and *in vivo* mouse micronucleus test and *in vitro* and *ex vivo* rat hepatocyte UDS assays. It, however, produced a significant increase in UDS in HeLa cells *in vitro* and a significant increased incidence of cells with polyploidy in an *in vitro* human lymphocyte chromosomal aberration test.

Granisetron at subcutaneous doses up to 6 mg/kg/day (36 mg/m²/day, 97 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy

Teratogenic Effects. Pregnancy Category B. Reproduction studies have been performed in pregnant rats at intravenous doses up to 9 mg/kg/day (54 mg/m²/day, 146 times the recommended human dose based on body surface area) and pregnant rabbits at intravenous doses up to 3 mg/kg/day (35.4 mg/m²/day, 96 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to granisetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether granisetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when *Kytril* Injection is administered to a nursing woman.

Pediatric Use

See DOSAGE AND ADMINISTRATION for use in children 2 to 16 years of age. Safety and effectiveness in children under 2 years of age have not been established.

Geriatric Use

During clinical trials, 713 patients 65 years of age or older received Kytril (granisetron HCl) Injection. Effectiveness and safety were similar in patients of various ages.

ADVERSE REACTIONS

The following have been reported during controlled clinical trials or in the routine management of patients. The percentage figures are based on clinical trial experience only. Table 7 gives the comparative frequencies of the five most commonly reported adverse events (≥3%) in patients receiving *Kytril* Injection, in single-day chemotherapy trials. These patients received chemotherapy, primarily cisplatin, and intravenous fluids during the 24-hour period following *Kytril* Injection administration. Events were generally recorded over seven days post-*Kytril* Injection administration. In the absence of a placebo group, there is uncertainty as to how many of these events should be attributed to *Kytril*, except for headache, which was clearly more frequent than in comparison groups.

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

	Percent of Patients with Event	
	Kytril Injection 40 mcg/kg (n=1,258)	Comparator[1] (n=422)
Headache	14%	6%
Asthenia	5%	6%
Somnolence	4%	15%
Diarrhea	4%	6%
Constipation	3%	3%

1. Metoclopramide/dexamethasone and phenothiazines/dexamethasone.

In over 3,000 patients receiving *Kytril* Injection (2 to 160 mcg/kg) in single-day and multiple-day clinical trials with emetogenic cancer therapies, adverse events, other than those in Table 7, were observed; attribution of many of these events to *Kytril* is uncertain.

Hepatic: In comparative trials, mainly with cisplatin regimens, elevations of AST and ALT (>2 times the upper limit of normal) following administration of *Kytril* Injection occurred in 2.8% and 3.3% of patients, respectively. These frequencies were not significantly different from those seen with comparators (AST: 2.1%; ALT: 2.4%).

Cardiovascular: Hypertension (2%); hypotension, arrhythmias such as sinus bradycardia, atrial fibrillation, varying degrees of A-V block, ventricular ectopy including nonsustained tachycardia, and ECG abnormalities have been observed rarely.

Central Nervous System: Agitation, anxiety, CNS stimulation and insomnia were seen in less than 2% of patients. Extrapyramidal syndrome occurred rarely and only in the presence of other drugs associated with this syndrome.

Hypersensitivity: Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylaxis, shortness of breath, hypotension, urticaria) have been reported.

Other: Fever (3%), taste disorder (2%), skin rashes (1%). In multiple-day comparative studies, fever occurred more frequently with *Kytril* Injection (8.6%) than with comparative drugs (3.4%, $P < 0.014$), which usually included dexamethasone.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

The recommended dosage for *Kytril* Injection is 10 mcg/kg administered intravenously within 30 minutes before initiation of chemotherapy, and only on the day(s) chemotherapy is given. *Kytril* Injection may be administered intravenously either undiluted over 30 seconds, or diluted with 0.9% Sodium Chloride or 5% Dextrose and infused over 5 minutes.

Pediatric Use: The recommended dose in children 2 to 16 years of age is 10 mcg/kg (see CLINICAL TRIALS). Children under 2 years of age have not been studied.

Use in the Elderly, Renal Failure Patients or Hepatically Impaired Patients: No dosage adjustment is recommended. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)

Infusion Preparation

Kytril Injection, administered as a 5-minute infusion, should be diluted in 0.9% Sodium Chloride or 5% Dextrose to a total volume of 20 to 50 mL.

Stability

Intravenous infusion of *Kytril* Injection should be prepared at the time of administration. However, *Kytril* Injection has been shown to be stable for at least 24 hours when diluted in 0.9% Sodium Chloride or 5% Dextrose and stored at room temperature under normal lighting conditions.

As a general precaution, *Kytril* Injection should not be mixed in solution with other drugs. Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

HOW SUPPLIED

Kytril (granisetron hydrochloride) Injection, 1 mg/mL (free base), is supplied in 1 mL Single-Use Vials and 4 mL Multi-Dose Vials.

NDC 0029-4149-01 (package of 1 Single-Dose Vial)
NDC 0029-4152-01 (package of 1 Multi-Dose Vial)

Store single-dose vials and multi-dose vials at 25°C (77°F); excursions permitted to 15–30°C (59–86°F).

Once the multi-dose vial is penetrated, its contents should be used within 30 days.

Do not freeze. Protect from light. Rx only

KY:L11A

Shown in Product Identification Guide, page 337

KYTRIL®

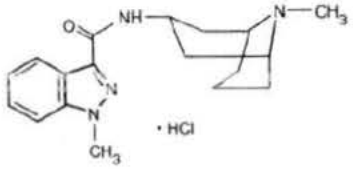
[kī '-tril]

granisetron hydrochloride

Tablets

DESCRIPTION

Kytril Tablets contain granisetron hydrochloride, an antinauseant and antiemetic agent. Chemically it is *endo*-N-(9-methyl-9-azabicyclo [3.3.1] non-3-yl)-1-methyl-1H-indazole-3-carboxamide hydrochloride with a molecular weight of 348.9 (312.4 free base). Its empirical formula is $C_{18}H_{24}N_4O \cdot HCl$, while its chemical structure is:



granisetron hydrochloride

Granisetron hydrochloride is a white to off-white solid that is readily soluble in water and normal saline at 20°C.

Tablets for Oral Administration: Each white, triangular, biconvex, film-coated *Kytril* Tablet contains 1.12 mg granisetron hydrochloride equivalent to granisetron, 1 mg. Inactive ingredients are: hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate and titanium dioxide.

CLINICAL PHARMACOLOGY

Granisetron is a selective 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT$_1$; 5-HT$_{1A}$; 5-HT$_{1BIC}$; 5-HT$_2$; for alpha$_1$-, alpha$_2$-, or beta-adrenoreceptors; for dopamine-D$_2$; or for histamine-H$_1$; benzodiazepine; picrotoxin, or opioid receptors.

Serotonin receptors of the 5-HT$_3$ type are located peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. During chemotherapy that induces vomiting, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT$_3$ receptors. This evokes vagal afferent discharge, inducing vomiting. Animal studies demonstrate that, in binding to 5-HT$_3$ receptors, granisetron blocks serotonin stimulation and subsequent vomiting after emetogenic stimuli such as cisplatin. In the ferret animal model, a single granisetron injection prevented vomiting due to high-dose cisplatin or arrested vomiting within 5 to 30 seconds.

In most human studies, granisetron has had little effect on blood pressure, heart rate or ECG. No evidence of an effect on plasma prolactin or aldosterone concentrations has been found in other studies.

Following single and multiple oral doses, *Kytril* slowed colonic transit in normal volunteers. However, *Kytril* had no effect on oro-cecal transit time in normal volunteers when given as a single intravenous (IV) infusion of 50 mcg/kg or 200 mcg/kg.