KYTRIL®

(granisetron hydrochloride)

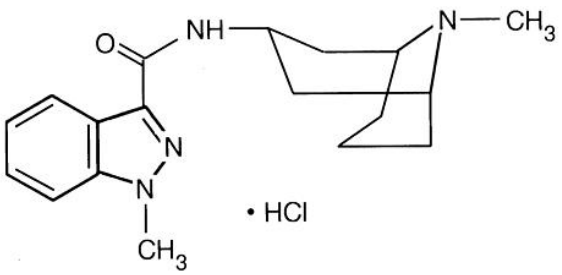
TABLETS

ORAL SOLUTION

R_x only

DESCRIPTION

KYTRIL Tablets and KYTRIL Oral Solution 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 $C_{18}H_{24}N_4O$•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 20ºC.

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.

Oral Solution

Each 10 mL of clear, orange-colored, orange-flavored KYTRIL Oral Solution contains 2.24 mg of granisetron hydrochloride equivalent to 2 mg granisetron. Inactive ingredients: citric acid anhydrous, FD&C Yellow No. 6, orange flavor, purified water, sodium benzoate, and sorbitol.

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$_{1B/C}$; 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 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 Tablets 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.

Pharmacokinetics

In healthy volunteers and adult cancer patients undergoing chemotherapy, administration of KYTRIL Tablets produced mean pharmacokinetic data shown in **Table 1**.

Table 1 Pharmacokinetic Parameters (Median [range]) Following KYTRIL Tablets (granisetron hydrochloride)

	Peak Plasma Concentration (ng/mL)	Terminal Phase Plasma Half-Life (h)	Volume of Distribution (L/kg)	Total Clearance (L/h/kg)
Cancer Patients 1 mg bid, 7 days (n=27)	5.99 [0.63 to 30.9]	N.D.[1]	N.D.	0.52 [0.09 to 7.37]
Volunteers single 1 mg dose (n=39)	3.63 [0.27 to 9.14]	6.23 [0.96 to 19.9]	3.94 [1.89 to 39.4]	0.41 [0.11 to 24.6]

[1] Not determined after oral administration; following a single intravenous dose of 40 mcg/kg, terminal phase half-life was determined to be 8.95 hours.

N.D. Not determined.

A 2 mg dose of KYTRIL Oral Solution is bioequivalent to the corresponding dose of KYTRIL Tablets (1 mg x 2) and may be used interchangeably.

Absorption

When KYTRIL Tablets were administered with food, AUC was decreased by 5% and C_{max} increased by 30% in non-fasted healthy volunteers who received a single dose of 10 mg.

Distribution

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

Metabolism

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

Elimination

Clearance is predominantly by hepatic metabolism. In normal volunteers, approximately 11% of the orally administered dose is eliminated unchanged in the urine in 48 hours. The remainder of the dose is excreted as metabolites, 48% in the urine and 38% in the feces.

Subpopulations

Gender

The effects of gender on the pharmacokinetics of KYTRIL Tablets have not been studied. However, after intravenous infusion of KYTRIL, no difference in mean AUC was found between males and females, although males had a higher C_{max} generally.

In elderly and pediatric patients and in patients with renal failure or hepatic impairment, the pharmacokinetics of granisetron was determined following administration of intravenous KYTRIL:

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.

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 with intravenous KYTRIL 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 dose, dosage adjustment in patients with possible hepatic functional impairment is not necessary.

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.

CLINICAL TRIALS

Chemotherapy-Induced Nausea and Vomiting

KYTRIL Tablets prevent nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, as shown by 24-hour efficacy data from studies using both moderately- and highly-emetogenic chemotherapy.

Moderately Emetogenic Chemotherapy

The first trial compared KYTRIL Tablets doses of 0.25 mg to 2 mg bid, in 930 cancer patients receiving, principally, cyclophosphamide, carboplatin, and cisplatin (20 mg/m^2 to 50 mg/m^2). Efficacy was based on complete response (ie, no vomiting, no moderate or severe nausea, no rescue medication), no vomiting, and no nausea. **Table 2** summarizes the results of this study.

Table 2 Prevention of Nausea and Vomiting 24 Hours Post-Chemotherapy[1]

	Percentages of Patients KYTRIL Tablet Dose			
Efficacy Measures	**0.25 mg bid (n=229) %**	**0.5 mg bid (n=235) %**	**1 mg bid (n=233) %**	**2 mg bid (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.

*Statistically significant (P<0.01) vs. 0.25 mg bid.

†Statistically significant (P<0.01) vs. 0.5 mg bid.

Results from a second double-blind, randomized trial evaluating KYTRIL Tablets 2 mg qd and KYTRIL Tablets 1 mg bid were compared to prochlorperazine 10 mg bid derived from a historical control. At 24 hours, there was no statistically significant difference in efficacy between the two KYTRIL Tablet regimens. Both regimens were statistically superior to the prochlorperazine control regimen (see **Table 3**).

Table 3 Prevention of Nausea and Vomiting 24 Hours Post-Chemotherapy[1]

	Percentages of Patients		
Efficacy Measures	**KYTRIL Tablets 1 mg bid (n = 354) %**	**KYTRIL Tablets 2 mg qd (n = 343) %**	**Prochlorperazine[2] 10 mg bid (n=111) %**
Complete Response[3]	69*	64*	41
No Vomiting	82*	77*	48
No Nausea	51*	53*	35
Total Control[4]	51*	50*	33

[1] Moderately emetogenic chemotherapeutic agents included cisplatin (20 mg/m^2 to 50 mg/m^2), oral and intravenous cyclophosphamide, carboplatin, dacarbazine, doxorubicin.

[2] Historical control from a previous double-blind KYTRIL trial.
[3] No vomiting, no moderate or severe nausea, no rescue medication.
[4] No vomiting, no nausea, no rescue medication.
*Statistically significant (P<0.05) vs. prochlorperazine historical control.

Results from a KYTRIL Tablets 2 mg qd alone treatment arm in a third double-blind, randomized trial, were compared to prochlorperazine (PCPZ), 10 mg bid, derived from a historical control. The 24-hour results for KYTRIL Tablets 2 mg qd were statistically superior to PCPZ for all efficacy parameters: complete response (58%), no vomiting (79%), no nausea (51%), total control (49%). The PCPZ rates are shown in **Table 3**.

Cisplatin-Based Chemotherapy

The first double-blind trial compared KYTRIL Tablets 1 mg bid, relative to placebo (historical control), in 119 cancer patients receiving high-dose cisplatin (mean dose 80 mg/m^2). At 24 hours, KYTRIL Tablets 1 mg bid was significantly (P<0.001) superior to placebo (historical control) in all efficacy parameters: complete response (52%), no vomiting (56%) and no nausea (45%). The placebo rates were 7%, 14%, and 7%, respectively, for the three efficacy parameters.

Results from a KYTRIL Tablets 2 mg qd alone treatment arm in a second double-blind, randomized trial, were compared to both KYTRIL Tablets 1 mg bid and placebo historical controls. The 24-hour results for KYTRIL Tablets 2 mg qd were: complete response (44%), no vomiting (58%), no nausea (46%), total control (40%). The efficacy of KYTRIL Tablets 2 mg qd was comparable to KYTRIL Tablets 1 mg bid and statistically superior to placebo. The placebo rates were 7%, 14%, 7%, and 7%, respectively, for the four parameters.

No controlled study comparing granisetron injection with the oral formulation to prevent chemotherapy-induced nausea and vomiting has been performed.

Radiation-Induced Nausea and Vomiting

Total Body Irradiation

In a double-blind randomized study, 18 patients receiving KYTRIL Tablets, 2 mg daily, experienced significantly greater antiemetic protection 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 three fractions on each of the first 3 days, and two fractions on the fourth day. KYTRIL Tablets were given one hour before the first radiation fraction of each day.

Twenty-two percent (22%) of patients treated with KYTRIL Tablets did not experience vomiting or receive rescue antiemetics over the entire 4-day dosing period, compared to 0% of patients in the historical negative control group (P<0.01).

In addition, patients who received KYTRIL 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 KYTRIL Tablets.

Fractionated Abdominal Radiation

The efficacy of KYTRIL Tablets, 2 mg daily, was evaluated in a double-blind, placebo-controlled randomized trial of 260 patients. KYTRIL 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.

The proportion of patients without emesis and those without nausea for KYTRIL Tablets, compared to placebo, was statistically significant ($P<0.0001$) at 24 hours after radiation, irrespective of the radiation dose. KYTRIL was superior to placebo in patients receiving up to 10 daily fractions of radiation, but was not superior to placebo in patients receiving 20 fractions.

Patients treated with KYTRIL Tablets (n=134) had a significantly longer time to the first episode of vomiting (35 days vs. 9 days, $P<0.001$) relative to those patients who received placebo (n=126), and a significantly longer time to the first episode of nausea (11 days vs. 1 day, $P<0.001$). KYTRIL provided significantly greater protection from nausea and vomiting than placebo.

INDICATIONS AND USAGE

KYTRIL (granisetron hydrochloride) is indicated for the prevention of:

- Nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin.
- Nausea and vomiting associated with radiation, including total body irradiation and fractionated abdominal radiation.

CONTRAINDICATIONS

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

PRECAUTIONS

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

Drug Interactions

Granisetron does not induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system in vitro. There have been no definitive drug-drug interaction studies to examine pharmacokinetic or pharmacodynamic interaction with other drugs; however, in humans,

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. No specific interaction studies have been conducted in anesthetized patients. In addition, the activity of the cytochrome P-450 subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by KYTRIL in vitro.

In in vitro human microsomal studies, ketoconazole inhibited ring oxidation of KYTRIL. However, the clinical significance of in vivo pharmacokinetic interactions with ketoconazole is not known. In a human pharmacokinetic study, hepatic enzyme induction with phenobarbital resulted in a 25% increase in total plasma clearance of intravenous KYTRIL. The clinical significance of this change is not known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month carcinogenicity study, rats were treated orally with granisetron 1, 5 or 50 mg/kg/day (6, 30 or 300 mg/m^2/day). The 50 mg/kg/day dose was reduced to 25 mg/kg/day (150 mg/m^2/day) during week 59 due to toxicity. For a 50 kg person of average height (1.46 m^2 body surface area), these doses represent 4, 20, and 101 times the recommended clinical dose (1.48 mg/m^2, oral) 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/m^2/day, 20 times the recommended human dose based on body surface area) and above, and in females treated with 25 mg/kg/day (150 mg/m^2/day, 101 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/m^2/day, 4 times the recommended human dose based on body surface area) in males and 5 mg/kg/day (30 mg/m^2/day, 20 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/m^2/day, 405 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) 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 oral doses up to 100 mg/kg/day (600 mg/m^2/day, 405 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 oral doses up to 125 mg/kg/day (750 mg/m^2/day, 507 times the recommended human dose based on body surface area) and pregnant rabbits at oral doses up to 32 mg/kg/day (378 mg/m^2/day, 255 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 is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

During clinical trials, 325 patients 65 years of age or older received KYTRIL Tablets; 298 were 65 to 74 years of age, and 27 were 75 years of age or older. Efficacy and safety were maintained with increasing age.

ADVERSE REACTIONS

Chemotherapy-Induced Nausea and Vomiting

Over 3700 patients have received KYTRIL Tablets in clinical trials with emetogenic cancer therapies consisting primarily of cyclophosphamide or cisplatin regimens.

In patients receiving KYTRIL Tablets 1 mg bid for 1, 7 or 14 days, or 2 mg qd for 1 day, adverse experiences reported in more than 5% of the patients with comparator and placebo incidences are listed in **Table 4**.

Table 4 Principal Adverse Events in Clinical Trials

	Percent of Patients With Event			
	KYTRIL[1] Tablets 1 mg bid (n=978)	**KYTRIL[1] Tablets 2 mg qd (n=1450)**	**Comparator[2] (n=599)**	**Placebo (n=185)**
Headache[3]	21%	20%	13%	12%
Constipation	18%	14%	16%	8%
Asthenia	14%	18%	10%	4%
Diarrhea	8%	9%	10%	4%
Abdominal pain	6%	4%	6%	3%
Dyspepsia	4%	6%	5%	4%

[1] Adverse events were recorded for 7 days when KYTRIL Tablets were given on a single day and for up to 28 days when KYTRIL Tablets were administered for 7 or 14 days.

[2] Metoclopramide/dexamethasone; phenothiazines/dexamethasone; dexamethasone alone; prochlorperazine.

[3] Usually mild to moderate in severity.

Other adverse events reported in clinical trials were:

Gastrointestinal: In single-day dosing studies in which adverse events were collected for 7 days, nausea (20%) and vomiting (12%) were recorded as adverse events after the 24-hour efficacy assessment period.

Hepatic: In comparative trials, elevation of AST and ALT (>2 times the upper limit of normal) following the administration of KYTRIL Tablets occurred in 5% and 6% of patients, respectively. These frequencies were not significantly different from those seen with comparators (AST: 2%; ALT: 9%).

Cardiovascular: Hypertension (1%); hypotension, angina pectoris, atrial fibrillation, and syncope have been observed rarely.

Central Nervous System: Dizziness (5%), insomnia (5%), anxiety (2%), somnolence (1%). One case compatible with, but not diagnostic of, extrapyramidal symptoms has been reported in a patient treated with KYTRIL Tablets.

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

Other: Fever (5%). Events often associated with chemotherapy also have been reported: leukopenia (9%), decreased appetite (6%), anemia (4%), alopecia (3%), thrombocytopenia (2%).

Over 5000 patients have received injectable KYTRIL in clinical trials.

Table 5 gives the comparative frequencies of the five commonly reported adverse events (≥3%) in patients receiving KYTRIL Injection, 40 mcg/kg, in single-day chemotherapy trials. These patients received chemotherapy, primarily cisplatin, and intravenous fluids during the 24-hour period following KYTRIL Injection administration.

Table 5 Principal Adverse Events in Clinical Trials — Single-Day Chemotherapy

	Percent of Patients with Event	
	KYTRIL Injection[1] 40 mcg/kg (n=1268)	**Comparator[2] (n=422)**
Headache	14%	6%
Asthenia	5%	6%
Somnolence	4%	15%
Diarrhea	4%	6%
Constipation	3%	3%

[1] Adverse events were generally recorded over 7 days post-KYTRIL Injection administration.

[2] Metoclopramide/dexamethasone and phenothiazines/dexamethasone.

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.

Radiation-Induced Nausea and Vomiting

In controlled clinical trials, the adverse events reported by patients receiving KYTRIL Tablets and concurrent radiation were similar to those reported by patients receiving KYTRIL Tablets prior to chemotherapy. The most frequently reported adverse events were diarrhea, asthenia, and constipation. Headache, however, was less prevalent in this patient population.

OVERDOSAGE

There is no specific treatment for granisetron hydrochloride 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

Emetogenic Chemotherapy

The recommended adult dosage of oral KYTRIL (granisetron hydrochloride) is 2 mg once daily or 1 mg twice daily. In the 2 mg once-daily regimen, two 1 mg tablets or 10 mL of KYTRIL Oral Solution (2 teaspoonfuls, equivalent to 2 mg of granisetron) are given up to 1 hour before chemotherapy. In the 1 mg twice-daily regimen, the first 1 mg tablet or one teaspoonful (5 mL) of KYTRIL Oral Solution is given up to 1 hour before chemotherapy, and the second tablet or second teaspoonful (5 mL) of KYTRIL Oral Solution, 12 hours after the first. Either regimen is administered only on the day(s) chemotherapy is given. Continued treatment, while not on chemotherapy, has not been found to be useful.

Use in the Elderly, Pediatric Patients, Renal Failure Patients or Hepatically Impaired Patients

No dosage adjustment is recommended (see **CLINICAL PHARMACOLOGY**: **Pharmacokinetics**).

Radiation (Either Total Body Irradiation or Fractionated Abdominal Radiation)

The recommended adult dosage of oral KYTRIL is 2 mg once daily. Two 1 mg tablets or 10 mL of KYTRIL Oral Solution (2 teaspoonfuls, equivalent to 2 mg of granisetron) are taken within 1 hour of radiation.

Pediatric Use

There is no experience with oral KYTRIL in the prevention of radiation-induced nausea and vomiting in pediatric patients.

Use in the Elderly

No dosage adjustment is recommended.

HOW SUPPLIED

Tablets

White, triangular, biconvex, film-coated tablets; tablets are debossed K1 on one face.

1 mg Unit of Use 2’s: NDC 0004-0241-33

1 mg Single Unit Package 20’s: NDC 0004-0241-26 (intended for institutional use only)

Storage

Store between 15º and 30ºC (59º and 86ºF). Keep container closed tightly. Protect from light.

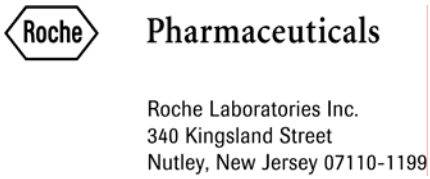
Oral Solution

Clear, orange-colored, orange-flavored, 2 mg/10 mL, in 30 mL amber glass bottles with child-resistant closures: NDC 0004-0237-09

Storage

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Keep bottle closed tightly and stored in an upright position. Protect from light.

Distributed by:



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