CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 77-297/S010

Name: Granisetron Hydrochloride Injection USP

Sponsor: Teva Parenteral Medicines, Inc.

Approval Date: April 13, 2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-297/S010

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-297/S010

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Rockville MD 20855

ANDA 077297/S-010

Teva Parenteral Medicines, Inc.
Attention: Sunni Churchill
Associate Director, Regulatory Affairs
10 Hughes
Irvine, CA 92618

Dear Madam:

This is in reference to your supplemental new drug application dated February 10, 2012, submitted pursuant to 21 CFR 314.70(c) (6) [Supplement – Changes Being Effected] for Granisetron Hydrochloride Injection USP, 1 mg (base)/mL, packaged in 4 mL Multi-Use Vials.

The supplemental new drug application provides for revisions to the insert labeling to be in accord with the labeling of Kytril® Intravenous Injection, approved April 29, 2011. Revisions were also made to the container label and carton labeling.

We have completed the review of your application and it is approved. However, please make the following revisions and submit as a Supplement – Changes Being Effected.

CONTAINER and CARTON

Please revise the abbreviation “I.V.” to read “Intravenous”.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the labeling of the reference listed drug with all differences annotated and explained.

We note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at

http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

PROMOTIONAL MATERIALS

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the following address or by facsimile at 301-847-8444:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

In addition, as required under 21 CFR 314.81(b)(3)(i), you must submit your updated final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA-2253, directly to the above address. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The materials submitted are being retained in our files.

Sincerely,

{See appended electronic signature page}

William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KOUNG U LEE
04/13/2012
For Wm. Peter Rickman

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-297/S010

LABELING

TEVA

(1 mg/mL)*

4 mg/4 mL

Granisetron HCl Injection USP

NDC 0703-7973-01 Rx only

NDC 0703-7973-01 Rx only

Granisetron HCl Injection USP

4 mg/4 mL

(1 mg/mL)*

For I.V. Use Only

4 mL Multi-Use Vial

Discard unused portion 30 days after vial penetration.

*Each mL contains, in sterile aqueous solution, 1.12 mg granisetron hydrochloride, equivalent to granisetron, 1 mg; sodium chloride, 9 mg; citric acid anhydrous, 2 mg; methylparaben, 1.8 mg and propylparaben, 0.2 mg as preservatives. Sodium hydroxide and hydrochloric acid, as pH adjusters.

Usual Dosage: See Package Insert.

Discard unused portion 30 days after vial penetration.

Rev. A 10/2011

Teva Pharmaceuticals USA
Sellersville, PA 18960

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature].
Do not freeze. Protect from light. Retain in carton until time of use.

See bottom panel for lot number and expiration date.

N 3 0703-7973-01 8

X12-X10-750

Reference ID: 3115038

NDC 0703-7973-01 Rx only

Granisetron
HCl Injection USP

4 mg/4 mL

(1 mg/mL)

For I.V. Use Only

4 mL Multi-Use Vial

Usual Dosage: See Package Insert.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature].

Do not freeze.

Protect from light.

Discard unused portion 28 days after initial penetration.

Teva Pharmaceuticals USA

Sellersville, PA 18960

Rev. A 10/2011

Y10709

TEVA

Package Insert

Rx only

Granisetron HCl Injection USP

7973
Rev. A 10/2011

TEVA

Y36-X10-751

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use granisetron hydrochloride injection USP safely and effectively. See full prescribing information for granisetron hydrochloride injection USP.

GRANISETRON hydrochloride injection USP, for intravenous use

Initial U.S. Approval: 1993

---- INDICATIONS AND USAGE ---

Granisetron hydrochloride injection USP is a serotonin-3 ($5\text{-}HT_3$) receptor antagonist indicated for:

- -Prevention of nausea and/or vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin. (1)

- DOSAGE AND ADMINISTRATION -

Prevention of chemotherapy-induced nausea and vomiting (2.1):

- -Recommended dosage is 10 mcg/kg intravenously within 30 minutes before initiation of chemotherapy
- -Pediatric patients (2 to 16 years): Recommended dosage is 10 mcg/kg

- DOSAGE FORMS AND STRENGTHS -

- Injection 1 mg/mL (free base). (3)

------ CONTRAINDICATIONS ------

- -Hypersensitivity to granisetron or to any of its components. (4)

- WARNINGS AND PRECAUTIONS -

- -Granisetron hydrochloride does not stimulate gastric or intestinal peristalsis and should not be used instead of nasogastric suction. (5.1)
- -QT prolongation has been reported with granisetron hydrochloride. Use with caution in patients with pre-existing arrhythmias or cardiac conduction disorders. (5.2)
- -Hypersensitivity reactions, such as anaphylaxis, shortness of breath, hypotension, and urticaria, may occur in patients with known hypersensitivity to other selective $5\text{-}HT_3$ receptor antagonists. (5.3)

------ ADVERSE REACTIONS ------

Most common adverse reactions:

- -Chemotherapy-induced nausea and vomiting (≥3%): Headache, and constipation (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact TEVA USA, PHARMACOVIGILANCE at 1-888-838-2872, X6351 or drug.safety@tevapharm.com; or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

------ DRUG INTERACTIONS ------

- -Granisetron hydrochloride injection has been administered safely with benzodiazepines, neuroleptics, and anti-ulcer medications. (7)
- -Does not appear to interact with emetogenic cancer chemotherapies. (7)
- -Inducers or inhibitors of CYP450 enzymes may change the clearance and therefore the half-life of granisetron. (7)
- Coadministration of granisetron hydrochloride with drugs known to prolong the QT interval and/or are arrhythmogenic may result in clinical consequences. (7)

- USE IN SPECIFIC POPULATIONS -

- -Pregnancy: Use only if clearly needed. (8.1)
- -Nursing mothers: Caution should be exercised when administered to a nursing woman. (8.3)
- -Geriatric use: No differences in responses between the elderly and younger patients were observed in reported clinical experience. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Granisetron hydrochloride injection USP is a serotonin-3 ($5\text{-}HT_3$) receptor antagonist indicated for:

- -The prevention of nausea and/or vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin.

2 DOSAGE AND ADMINISTRATION

2.1 Prevention of Chemotherapy-Induced Nausea and Vomiting

Adult Patients

The recommended dosage for granisetron hydrochloride injection USP is 10 mcg/kg administered intravenously within 30 minutes before initiation of chemotherapy, and only on the day(s) chemotherapy is given.

Infusion Preparation

Granisetron hydrochloride injection USP may be administered intravenously either undiluted over 30 seconds, or diluted with 0.9% Sodium Chloride or 5% Dextrose and infused over 5 minutes.

Stability

Intravenous infusion of granisetron hydrochloride injection USP should be prepared at the time of administration. However, granisetron hydrochloride injection USP 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, granisetron hydrochloride injection USP should not be mixed in solution with other drugs. Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

Pediatric Patients

The recommended dose in pediatric patients 2 to 16 years of age is 10 mcg/kg [*see Clinical Studies (14)*]. Pediatric patients under 2 years of age have not been studied.

3 DOSAGE FORMS AND STRENGTHS

Multi-Use Vials for Injection: 4 mg/4 mL

4 CONTRAINDICATIONS

Granisetron hydrochloride injection is contraindicated in patients with known hypersensitivity (eg. anaphylaxis, shortness of breath, hypotension, urticaria) to the drug or to any of its components.

5 WARNINGS AND PRECAUTIONS

5.1 Gastric or Intestinal Peristalsis

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 following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distention.

5.2 Cardiovascular Events

An adequate QT assessment has not been conducted, but QT prolongation has been reported with granisetron hydrochloride. Therefore, granisetron hydrochloride should be used with caution in patients with pre-existing arrhythmias or cardiac conduction disorders, as this might lead to clinical consequences. Patients with cardiac disease, on cardio-toxic chemotherapy, with concomitant electrolyte abnormalities and/or on concomitant medications that prolong the QT interval are particularly at risk.

5.3 Hypersensitivity Reactions

Hypersensitivity reactions (eg. anaphylaxis, shortness of breath, hypotension, urticaria) may occur in patients who have exhibited hypersensitivity to other selective $5\text{-}HT_3$ receptor antagonists.

6 ADVERSE REACTIONS

QT prolongation has been reported with granisetron hydrochloride [*see Wa nings and Precautions (5.2) and Drug Interactions (7)*].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in patients.

Chemotherapy-Induced Nausea and Vomiting

The following have been reported during controlled clinical trials or in the routine management of patients. The percentage figures are based on clinical trial experience only. Table 1 gives the comparative frequencies of the two most commonly reported adverse reactions (≥3%) in patients receiving granisetron hydrochloride injection, in single-day chemotherapy trials. These patients received chemotherapy, primarily cisplatin, and intravenous fluids during the 24-hour period following granisetron hydrochloride injection administration. Reactions were generally recorded over seven days post-granisetron hydrochloride injection administration.

Table 1 Principal Adverse Reactions in Clinical Trials — Single-Day Chemotherapy

	Percent of Patients With Reaction	
	Granisetron Hydrochloride Injection 40 mcg/kg (n=1268)	**Comparator[a] (n=422)**
Headache	14%	6%
Constipation	3%	3%

[a] Metoclopramide/dexamethasone and phenothiazines/dexamethasone.

Additional adverse events reported in clinical trials were asthenia, somnolence and diarrhea.

In over 3,000 patients receiving granisetron hydrochloride injection (2 to 160 mcg/kg) in single-day and multiple-day clinical trials with emetogenic cancer therapies, adverse events, other than those adverse reactions listed in Table 1, were observed; attribution of many of these events to granisetron hydrochloride 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 granisetron hydrochloride injection occurred in 2.8% and 3.3% of patients, respectively. These frequencies were not significantly different from those seen with comparators (AST: 2.1%; ALT: 2.4%).

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

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

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

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of granisetron hydrochloride. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to granisetron hydrochloride exposure.

QT prolongation has been reported with granisetron hydrochloride [*see Wa nings and Precautions (5.2) and Drug Interactions (7)*].

7 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, granisetron hydrochloride injection has been safely administered with drugs representing benzodiazepines, neuroleptics and anti-ulcer medications commonly prescribed with antiemetic treatments. Granisetron hydrochloride 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 granisetron hydrochloride *in vitro*.

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

QT prolongation has been reported with granisetron hydrochloride. Use of granisetron hydrochloride in patients concurrently treated with drugs known to prolong the QT interval and/or are arrhythmogenic may result in clinical consequences.

8 USE IN SPECIFIC POPULATIONS

8.1 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/m^2/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/m^2/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.

8.3 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 granisetron hydrochloride injection is administered to a nursing woman.

8.4 Pediatric Use

Chemotherapy-Induced Nausea and Vomiting

[*See Dosage and Administration (2)*] for use in chemotherapy-induced nausea and vomiting in pediatric patients 2 to 16 years of age. Safety and effectiveness in pediatric patients under 2 years of age have not been established.

8.5 Geriatric Use

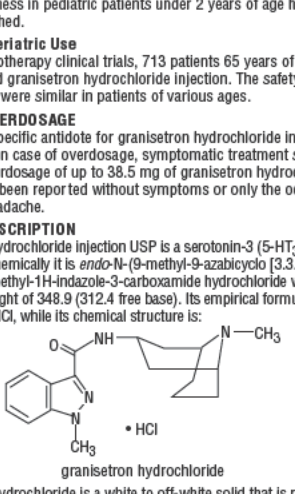
During chemotherapy clinical trials, 713 patients 65 years of age or older received granisetron hydrochloride injection. The safety and effectiveness were similar in patients of various ages.

10 OVERDOSAGE

There is no specific antidote for 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.

11 DESCRIPTION

Granisetron hydrochloride injection USP is a serotonin-3 ($5\text{-}HT_3$) receptor antagonist. 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. Granisetron hydrochloride injection USP is a clear, colorless, sterile, nonpyrogenic, aqueous solution for intravenous administration.

Granisetron hydrochloride injection USP, 1 mg/mL is available in a 4 mL multi-use vial.

Each 1 mL contains 1.12 mg granisetron hydrochloride equivalent to granisetron, 1 mg; sodium chloride, 9 mg; citric acid anhydrous, 2 mg; methylparaben, 1.8 mg and propylparaben, 0.2 mg, as preservatives, water for injection, USP q.s., sodium hydroxide and hydrochloric acid, as pH adjusters. The solution's pH ranges from 4.0 to 6.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Granisetron is a selective 5-hydroxytryptamine$_3$ ($5\text{-}HT_3$) receptor antagonist with little or no affinity for other serotonin receptors, including $5\text{-}HT_1$; $5\text{-}HT_{1A}$; $5\text{-}HT_{1B/C}$; $5\text{-}HT_2$; 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 $5\text{-}HT_3$ 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 $5\text{-}HT_3$ receptors. This evokes vagal afferent discharge and may induce vomiting. Animal studies demonstrate that, in binding to $5\text{-}HT_3$ 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.

Granisetron hydrochloride 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.

12.3 Pharmacokinetics

Chemotherapy-Induced Nausea and Vomiting

In adult cancer patients undergoing chemotherapy and in volunteers, mean pharmacokinetic data obtained from an infusion of a single 40 mcg/kg dose of granisetron hydrochloride injection are shown in Table 3.

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)	Total Clearance (L/h/kg)	Volume of Distribution (L/kg)
Cancer Patients				
Mean	63.8[a]	8.95[a]	0.38[a]	3.07[a]
Range	18.0 to 176	0.90 to 31.1	0.14 to 1.54	0.85 to 10.4
Volunteers 21 to 42 years				
Mean	64.3[b]	4.91[b]	0.79[b]	3.04[b]
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[b]	7.69[b]	0.44[b]	3.97[b]
Range	14.6 to 153	2.65 to 17.7	0.17 to 1.06	1.75 to 7.01

[a] 5-minute infusion.

[b] 3-minute infusion.

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 $5\text{-}HT_3$ receptor antagonist activity.

Elimination

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

Subpopulations

Gender

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

Elderly
The ranges of the pharmacokinetic parameters in elderly volunteers (mean age 71 years), given a single 40 mcg/kg intravenous dose of granisetron hydrochloride injection, were generally similar to those in younger healthy volunteers; mean values were lower for clearance and longer for half-life in the elderly patients (see Table 3).

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

Hepatically Impaired Patients
A pharmacokinetic study in patients with hepatic impairment due to neoplastic liver involvement showed that total clearance was approximately halved compared to patients without hepatic impairment. Given the wide variability in pharmacokinetic parameters noted in patients, dosage adjustment in patients with hepatic functional impairment is not necessary.

13 NONCLINICAL TOXICOLOGY

13.1 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 16, 81 and 405 times the recommended clinical dose (0.37 mg/m^2, iv) on a body surface area basis. There was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in males treated with 5 mg/kg/day (30 mg/m^2/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/m^2/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/m^2/day, 16 times the recommended human dose based on body surface area) in males and 5 mg/kg/day (30 mg/m^2/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/m^2/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, granisetron hydrochloride injection should be prescribed only at the dose and for the indication recommended [*see Indications and Usage (1) and Dosage and Administration (2)*].

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

Granisetron at subcutaneous doses up to 6 mg/kg/day (36 mg/m^2/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.

14 CLINICAL STUDIES

14.1 Chemotherapy-Induced Nausea and Vomiting

Single-Day Chemotherapy
Cisplatin-Based Chemotherapy
In a double-blind, placebo-controlled study in 28 cancer patients, granisetron hydrochloride injection, administered as a single intravenous infusion of 40 mcg/kg, was significantly more effective than placebo in preventing nausea and vomiting induced by cisplatin chemotherapy (see Table 5).

Table 5 Prevention of Chemotherapy-Induced Nausea and Vomiting — Single-Day Cisplatin Therapy[a]

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

[a] Cisplatin administration began within 10 minutes of granisetron hydrochloride injection infusion and continued for 1.5 to 3.0 hours. Mean cisplatin dose was 86 mg/m^2 in the granisetron hydrochloride injection group and 80 mg/m^2 in the placebo group.

[b] No vomiting and no moderate or severe nausea.

Granisetron hydrochloride 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. Granisetron hydrochloride injection doses of 10 and 40 mcg/kg were superior to 2 mcg/kg in preventing cisplatin-induced nausea and vomiting, but 40 mcg/kg was not significantly superior to 10 mcg/kg (see Table 6).

Table 6 Prevention of Chemotherapy-Induced Nausea and Vomiting — Single-Day High-Dose Cisplatin Therapy[a]

	Granisetron Hydrochloride Injection (mcg/kg)			P-Value (vs. 2 mcg/kg)	
	2	10	40	10	40
Number of Patients	52	52	53		
Response Over 24 Hours					
Complete Response[b]	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

[a] Cisplatin administration began within 10 minutes of granisetron hydrochloride injection infusion and continued for 2.6 hours (mean). Mean cisplatin doses were 96 to 99 mg/m^2.

[b] No vomiting and no moderate or severe nausea.

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 7.

Table 7 Prevention of Chemotherapy-Induced Nausea and Vomiting — Single-Day High-Dose and Low-Dose Cisplatin Therapy[a]

	Granisetron Hydrochloride Injection (mcg/kg)				P-Value (vs. 5 mcg/kg)		
	5	10	20	40	10	20	40
High-Dose Cisplatin							
Number of Patients	40	49	48	47			
Response Over 24 Hours							
Complete Response[b]	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[b]	29%	56%	58%	41%	0.012	0.009	NS
No Vomiting	36%	63%	65%	43%	0.012	0.008	NS
No Nausea	29%	56%	38%	33%	0.012	NS	NS

[a] Cisplatin administration began within 10 minutes of granisetron hydrochloride injection infusion and continued for 2 hours (mean). Mean cisplatin doses were 64 and 98 mg/m^2 for low and high strata.

[b] No vomiting and no use of rescue antiemetic.

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

Moderately Emetogenic Chemotherapy
Granisetron hydrochloride injection, 40 mcg/kg, was compared with the combination of chlorpromazine (50 to 200 mg/24 hours) and dexamethasone (12 mg) in patients treated with moderately emetogenic chemotherapy, including primarily carboplatin >300 mg/m^2, cisplatin 20 to 50 mg/m^2 and cyclophosphamide >600 mg/m^2. Granisetron hydrochloride injection was superior to the chlorpromazine regimen in preventing nausea and vomiting (see Table 8).

Table 8 Prevention of Chemotherapy-Induced Nausea and Vomiting— Single-Day Moderately Emetogenic Chemotherapy

	Granisetron Hydrochloride Injection	Chlorpromazine[a]	P-Value
Number of Patients	133	133	
Response Over 24 Hours			
Complete Response[b]	68%	47%	<0.001
No Vomiting	73%	53%	<0.001
No More Than Mild Nausea	77%	59%	<0.001

[a] Patients also received dexamethasone, 12 mg.

[b] No vomiting and no moderate or severe nausea.

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

Repeat-Cycle Chemotherapy
In an uncontrolled trial, 512 cancer patients received granisetron hydrochloride injection, 40 mcg/kg, prophylactically, for two cycles of chemotherapy, 224 patients received it for at least four cycles, and 108 patients received it for at least six cycles. Granisetron hydrochloride injection efficacy remained relatively constant over the first six repeat cycles, with complete response rates (no vomiting and no moderate or severe nausea in 24 hours) of 60% to 69%. No patients were studied for more than 15 cycles.

Pediatric Studies
A randomized double-blind study evaluated the 24-hour response of 80 pediatric cancer patients (age 2 to 16 years) to granisetron hydrochloride injection 10, 20 or 40 mcg/kg. Patients were treated with cisplatin ≥60 mg/m^2, cytarabine ≥3 g/m^2, cyclophosphamide ≥1 g/m^2 or nitrogen mustard ≥6 mg/m^2 (see Table 9).

Table 9 Prevention of Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients

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

[a] No vomiting and no moderate or severe nausea.

A second pediatric study compared granisetron hydrochloride injection 20 mcg/kg to chlorpromazine plus dexamethasone in 88 patients treated with ifosfamide ≥3 g/m^2/day for two or three days. Granisetron hydrochloride injection was administered on each day of ifosfamide treatment. At 24 hours, 22% of granisetron hydrochloride injection patients achieved complete response (no vomiting and no moderate or severe nausea in 24 hours) compared with 10% on the chlorpromazine regimen. The median number of vomiting episodes with granisetron hydrochloride injection was 1.5; with chlorpromazine it was 7.0.

16 HOW SUPPLIED/STORAGE AND HANDLING

Granisetron hydrochloride injection USP is supplied as follows:

NDC Number	Contents	Package size
0703-7973-01	4 mg/4 mL (free base)	4 mL multi-use vial packaged individually

Storage
Store multi-use vial at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

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

Do not freeze. Protect from light. Retain in carton until time of use.

17 PATIENT COUNSELING INFORMATION

Patients should be informed that the most common adverse reactions for the indication of chemotherapy induced nausea and vomiting are headache and constipation (see Table 1).

Patients should be advised of the risk of allergic reactions if they have a prior allergic reaction to a class of antiemetics known as 5-HT$_3$ receptor antagonists.

Electrocardiogram changes (QT prolongation) have been reported with the use of granisetron hydrochloride. Patients should be cautioned about the use of this drug if they have heart problems or take medications for heart problems.

Rev. A 10/2011

Teva Pharmaceuticals USA
Sellersville, PA 18960

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-297/S010

LABELING REVIEWS

Labeling Review Branch
Division of Labeling and Program Supports
Office of Generic Drugs

Labeling Supplement Review

Application Number: 077297/S-010

Name of Drug: Granisetron Hydrochloride Injection USP, 1 mg (base)/mL, 4 mL Multi-Use Vial

Applicant: TEVA Parenteral Medicines, Inc.

Material Reviewed:
Submission Date(s): February 10, 2012
CBE-0 Submission: Insert, Container, Carton

Background and Summary

1. Background: ANDA was approved June 30, 2008. S-010 is the first labeling supplement for this ANDA. This ANDA is the new RLD for Granisetron Hydrochloride Injection USP, 1 mg (base)/mL, packaged in 4 mL Multi-Use Vials. The brand name, Kytril® Intravenous Injection (NDA 020239) has been discontinued.

2. This supplemental application provides for revisions to the insert labeling to be in accord with the reference listed drug, Kytril® Intravenous Injection, approved April 29, 2011. Revisions were also made to the container label and carton labeling.

3. Model Labeling: Teva is the RLD.
   The last approved labeling for Teva's ANDA 077297 was approved with the original application on June 30, 2008, and is based on the labeling of Kytril® Intravenous Injection by Roche (NDA 020239/S-018), approved November 23, 2005. Since this date, Granisetron Hydrochloride Injection became a product of a USP Monograph and two additional labeling supplements were approved for Kytril® Intravenous Injection. NDA 020239/S-021 was approved on October 7, 2007 with revisions to the Precautions and Adverse Reaction sections of the package insert. NDA 020239/S-023 was approved on April 29, 2011 with conversion of the package insert to the Physician Labeling Rule format and with updates to the insert labeling with information from pediatric study report ML16633 "Intravenous Granisetron (Kytril) in the Prevention of Post-operative Nausea and Vomiting (PONV) in Pediatric Subjects Undergoing Tonsillectomy or Adenotonsillectomy." Revisions were also made to the container label and carton labeling.

4. USP (checked 4/6/12) - Granisetron Hydrochloride Injection
   Packaging and storage— Preserve in single-dose or multiple-dose containers, protected from light, and store at controlled room temperature.
   Labeling— It meets the requirements for *Labeling* under *Injections* 1 . Label it to indicate the name and the quantity of any added preservative.

5. Patent/Exclusivity:

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Certification	Labeling Impact	Patent Use Code
N020239	001	5952340	Sep 14, 2016	MOU	Carved out	U - 519
N020239	001	6294548	May 4, 2019	PIV	none	

Code	Definition
U - 519	POST OPERATIVE NAUSEA AND VOMITING

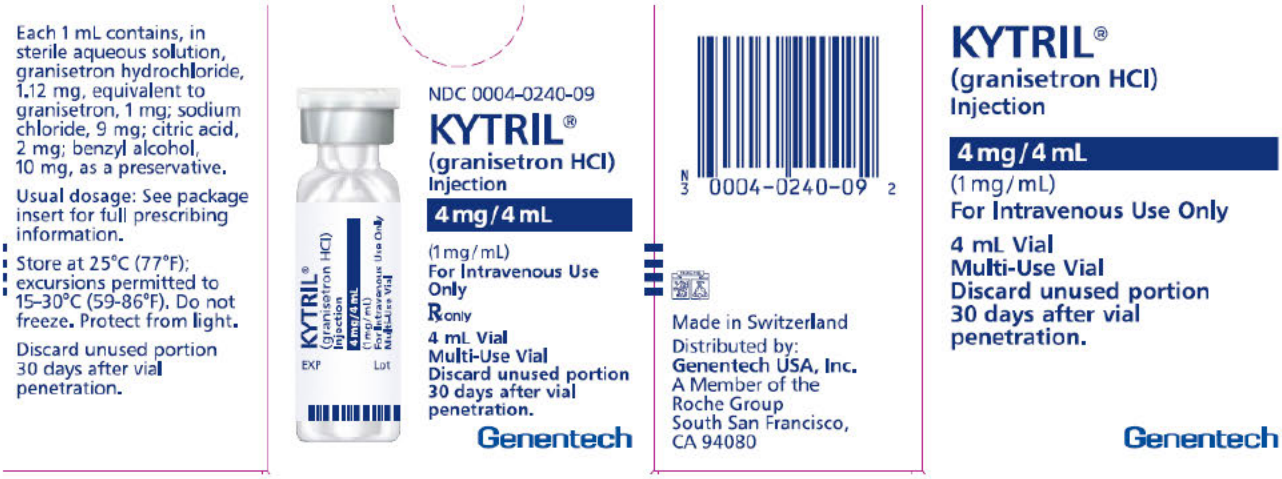
Exclusivity Data

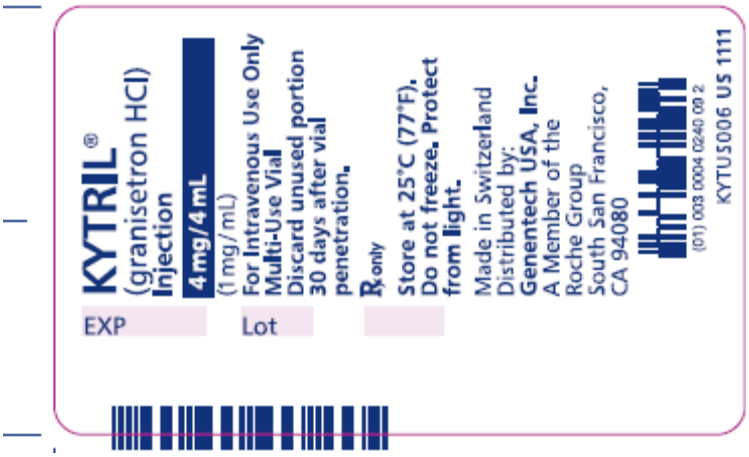
Appl No	Prod No	Exclusivity Code/Impact	Exclusivity Expiration
N020239	001	M - 102 (carved out)	Apr 29, 2014

Code	Definition
M - 102	INFORMATION FROM PEDIATRIC STUDY REPORT ML16633, "INTRAVENOUS GRANISETRON (KYTRIL) IN THE PREVENTION OF POST-OPERATIVE NAUSEA AND VOMITING (PONV) IN PEDIATRIC SUBJECTS UNDERGOING TONSILLECTOMY OR ADENOTONSILLECTOMY."

Review

Teva revised the insert labeling to be in accord with the labeling of Kytril® Intravenous Injection, approved April 29, 2011. Teva also revised the established name from "Granisetron HCl Injection" to "Granisetron HCl Injection USP" on the insert, container and carton labeling per the current USP monograph. Teva revised the container and carton labeling with the addition of the statement "Discard unused portion 30 days after vial penetration" as per the label/labeling of Kytril approved on April 29, 2011.





The submitted labels and labeling are acceptable for approval. Will ask firm to revise the abbreviation "I.V." to read "Intravenous" on the container label and carton labeling. Per DMEPA's review dated 10/29/2010 in DARRTS under NDA 020239/S-023, the abbreviation for intravenous is considered an error-prone abbreviation. "As part of a national campaign to warn healthcare practitioners and consumers not to use error-prone abbreviations, acronyms, dose designations, or symbols, including trailing zeroes, FDA agreed not to use such error prone designations in their approved product labeling."

CONTAINER and CARTON

Please revise the abbreviation "I.V." to read "Intravenous".

Recommendation

Recommend approval.

{see appended electronic signature}

Lisa Kwok
Labeling Reviewer

Supervisory Comment/Concurrence:

{see appended electronic signature}

Koung Lee
Team Leader

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LISA H KWOK
04/11/2012

KOUNG U LEE
04/13/2012
For Wm. Peter Rickman