Granisetron hydrochloride is a selective 5-hydroxytryptamine (5-HT3) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT1A, 5-HT2A, 5-HT2C, 5-HT4, 5-HT6, 5-HT7, and alpha2-, beta-, and alpha1-adreceptors; for dopamine-D2 or -D3, histamine H1, benzodiazepine, or opioid receptors.

**CLINICAL PHARMACOLOGY**

Granisetron is a selective 5-hydroxytryptamine (5-HT3) receptor antagonist. It differs from such compounds as metoclopramide, domperidone, and cisapride in that it does not cause gastric emptying, but rather inhibits gastric and intestinal motility, which is mediated by the 5-HT3 receptor located on vagal afferent fibers. Onset of action is within 30–60 minutes. The duration of action ranges from 6 to 12 hours with controlled-release tablets.

In humans, granisetron is rapidly absorbed after oral or intravenous administration and is extensively metabolized in the liver. The major metabolite is 4-hydroxy granisetron. Following oral administration, maximum plasma concentrations are achieved within 0.5–2 hours of dosing. The volume of distribution in an adult volunteer with a normal body weight of 70 kg is about 700 L. The plasma elimination half-life is approximately 8 hours. Granisetron is eliminated primarily in the urine (48%) and to a lesser extent in the feces (38%). The remainder of the dose is excreted as metabolites, 6% in the urine and 3% in the feces.

**INDICATIONS AND USAGE**

Granisetron hydrochloride is indicated for the prevention of nausea and vomiting associated with cisplatin-based chemotherapy and for the prevention of chemotherapy-induced nausea and vomiting in patients undergoing abdominal irradiation.

Granisetron hydrochloride is also indicated for the acute treatment of nausea and vomiting associated with radiation therapy for non-malignant indications, and for the treatment of acute and recurrent emesis following abdominal surgery.
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 isozyme 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by granisetron in vitro.

In vitro human microsomal studies, ketocconazole inhibited ring oxidation of granisetron. However, the clinical significance of in vitro 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. 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 arrhythmicogenic, this may result in clinical consequences.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24 month carcinogenicity study, rats were treated orally with granisetron hydrochloride, 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 (1.46 m2 body surface area), these doses represent 4, 20, and 101 times the recommended clinical dose (1.48 mg/m2, 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/m2/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/m2/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/m2/day, 4 times the recommended human dose based on body surface area) in males and 5 mg/kg/day (30 mg/m2/day, 30 times the recommended human dose based on body surface area) in females. In a 12 month oral toxicity study, treatment with granisetron hydrochloride, 100 mg/kg/day (600 mg/m2/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 carcinosogeny 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 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 vivo and ex vivo rat hepatocyte UDS assays. However, it produced a significant increase in UDS in Hela cells in vitro and a significant increased incidence of cells with polyplody in an in vitro human lymphocyte chromosomal aberration test. Carcinogenicity, mutagenesis, and carcinogenicity in vivo 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, paranoid ideations and hallucinations was reported.

Granisetron at oral doses up to 100 mg/kg/day (600 mg/m2/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.

Teratogenic Effects

Reproduction category B

Reproduction studies have been performed in pregnant rats at oral doses up to 125 mg/kg/day (750 mg/m2/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/m2/day, 355 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 granisetron hydrochloride is administered to a nursing woman. Many drugs are excreted in human milk, caution should be exercised when granisetron hydrochloride is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Safety and effectiveness in pediatrics have not been established. Use in the Elderly

Radiation-induced Nausea and Vomiting

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

Postmarketing Experience

Gastrointestinal Symptoms

In a 12 month clinical trial, the adverse events reported by patients taking granisetron tablets were administered for 7 or 14 days. The most frequently reported adverse events were diarrhea, constipation and headache. Other adverse events reported in less than 5% of patients taking granisetron tablets were vomiting, flatulence, vertigo, sweating, visual disturbance, visual disturbance, fever, increased appetite, weight gain, decreased appetite, and weight loss.

OVERDOSE

There is no specific treatment for granisetron hydrochloride overdose. In case of overdose, symptomatic treatment should be given.

DOSAGE AND ADMINISTRATION

Granisetron hydrochloride tablets are USP, 1 mg and 2 mg tablets are given up to 1 hour before chemotherapy. In the 1 mg twice-daily regimen, the first 1 mg tablet is given up to 1 hour before chemotherapy, and the second granisetron hydrochloride tablets are given after chemotherapy, with at least 2 hours in between. Either regimen is administered only on the day of chemotherapy. In store, treatment, not on chemotherapy, has not been found to be useful.

USE IN THE ELDERLY, RENAL FAILURE PATIENTS OR HEPATIC IMPAIRED PATIENTS

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Topical Use

No dosage adjustment is recommended. USE IN THE ELDERLY, RENAL FAILURE PATIENTS OR HEPATIC IMPAIRED PATIENTS

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

How Supplied

Granisetron hydrochloride tablets USP are available as:

1 mg, white to off-white, film-coated, capsule-shaped tablet, debossed with the number “93” on one side and “7485” on the other. They are available in blister cards of 2 (1 card of 2 unit dose tablets) and blister cards of 20 (4 cards of 5 unit dose tablets) each. Store at 20° to 25° C (68° to 77° F); [USP Controlled Room Temperature]. Keep container closed tightly. Protect from light.

Manufactured in Israel by:

TEVA PHARMACEUTICAL INDU. LTD.
Jerusalem, 91010, Israel

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Rev: C 12/2011
322K003827112

Reference ID: 3113507