Sitensa™

(Granisetron HCl)
Oral Solution

1mg/5mL

سیٹنسا

(گرینی سیٹرون ایچ سی ایل)
اورل سلوشن
۱ ملی گرام/ ۵ ملی لیٹر

QUALITATIVE AND QUANTITATIVE COMPOSITION

Sitensa Oral Solution: Each 5mL contains: Granisetron Hydrochloride U.S.P eq. to Granisetron.....1mg
Innovator's Specification

DESCRIPTION

Sitensa oral solution contains a medicine called granisetron (as hydrochloride). It is an antinauseant and antiemetic agent used to treat nausea and vomiting following chemotherapy and radiotherapy.

CLINICAL PHARMACOLOGY

Pharmacodynamics: Mechanism of Action: Granisetron is a selective 5-hydroxytryptamine3 (5-HT3) receptor antagonist with little or no affinity for other serotonin receptors. During chemotherapy that induces vomiting, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT3 receptors. This evokes vagal afferent discharge, inducing vomiting. Animal studies demonstrate that, in binding to 5-HT3 receptors, granisetron blocks serotonin stimulation and subsequent vomiting after emetogenic stimuli such as cisplatin.

Pharmacokinetics: Absorption: When granisetron Tablets were administered with food, AUC was decreased by 5% and Cmax increased by 30% in non-fasted healthy volunteers who received a single dose of 10mg.

Distribution: Plasma protein binding is approximately 65% and granisetron distributes freely between 60 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-HT3 receptor antagonist activity.

Excretion: 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.

INDICATIONS

Granisetron is indicated for the prevention of:

- Nausea and vomiting associated with initial and repeat courses of emetogenic cancer 181 therapy, including high-dose cisplatin.
- Nausea and vomiting associated with radiation, including total body irradiation and 183 fractionated abdominal radiation.

CONTRAINDICATIONS

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

INTERACTIONS

Effects of granisetron on other medicinal products: 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, grani-setron Injection has been safely administered with drugs representing benzodiazepines, neuroleptics, and anti-ulcer medications commonly prescribed with antiemetic treatments. GRANISETRON 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 (in-volved in the metabolism of some of the main narcotic analgesic agents) is not modified by GRANISETRON in vitro.

Effects of other medicinal products on granisetron: In in vitro human microsomal studies, ketoconazole inhibited ring oxidation of granisetron. 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. 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 50mg/kg/day (6, 30 or 300mg/m2/-day). The 50mg/kg/day dose was reduced to 25mg/kg/day (150mg/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 (1.48mg/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 5mg/kg/day (30mg/m2/day, 20 times the recommended human dose based on body surface area) and above, and in females treated with 25mg/kg/day (150mg/m2/day, 101 times the rec-ommended human dose based on body surface area). No increase in liver tumors was observed at a dose of 1mg/kg/day (6mg/ m2/day, 4 times the recommended human dose based on body surface area) in males and 5mg/kg/day (30mg/m2/day, 20 times the recommended human dose based on body surface area) in females. In a 12-month oral toxicity study, treatment with granisetron 100mg/kg/day (600mg/ 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 carcinogen-icity 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 should be prescribed only at the dose and for the indication recommended. 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 aber-ration test. Granisetron at oral doses up to 100mg/kg/day (600mg/ m2/day, 405 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive perfor-mance of male and female rats.

USE IN SPECIFIC POPULATION

Pregnancy: Teratogenic effects: Pregnancy Category B Reproduction studies have been performed in pregnant rats at oral doses up to 125mg/kg/day (750mg/m_2/day, 507 times the recommended human dose based on body surface area) and pregnant rabbits at oral doses up to 32mg/kg/day (378mg/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 granisetron is ad ministered to a nursing woman.

Paediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Efficacy and safety were maintained with increasing age.

ADVERSE REACTIONS

Chemotherapy-Induced Nausea and Vomiting Over 3700 patients have received granisetron Tablets in clinical trials with emetogenic cancer therapies consisting primarily of cyclophos-phamide or cisplatin regimens. In patients receiving granisetron Tablets 1mg bid for 1, 7 or 14 days, or 2mg qd for 1 day, adverse experi-ences reported in more than 5% of the patients with comparator and placebo incidences are Headache, Constipation, Asthenia, Diarrhea, Abdominal pain, Dyspepsia.

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 GRANISETRON Tablets occurred in 5% and 6% of patients, re-spectively. These frequencies were not significantly different from those seen with compara-tors (AST: 2%; ALT: 9%).

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

Central Nervous System: Dizziness (5%), insomnia (5%), anxiety (2%), somnolence (1%). One case compat-ible with, but not diagnostic of, extrapyramidal symptoms has been report-ed in a patient treated with GRANISETRON Tablets.

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

Other: Fever (5%). Events often associated with chemotherapy also have been reported: leu-kopenia (9%), decreased appetite (6%), anemia (4%), alopecia (3%), thrombocytopenia (2%). Over 5000 patients have received injectable granisetron in clinical trials. In the absence of a placebo group, there is uncertainty as to how many of these events should be attributed to GRANISETRON, 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 GRANISETRON Tablets and concurrent radiation were similar to those reported by patients receiving GRANISETRON Tablets prior to chemotherapy. The most frequently reported adverse events were diarrhea, asthenia, and constipation. Headache, however, was less prevalent in this patient population.

DOSAGE AND ADMINISTRATION

Emetogenic Chemotherapy: The recommended adult dosage of oral GRANISETRON is 2mg once daily or 1mg twice daily. In the 2mg once-daily regimen, two 1mg tablets or 10mL of GRANISETRON Oral Solution (2 teaspoonfuls, equivalent to 2mg of granisetron) are given up to 1 hour before chemotherapy. In the 1mg twice-daily regimen, the first 1mg tablet or one teaspoonful (5 mL) of GRANISETRON Oral Solution is given up to 1 hour before chemother-apy, and the second tablet or second teaspoonful (5 mL) of GRANISETRON 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 rec-ommended.

Radiation (Either Total Body Irradiation or Fractionated Abdominal Radiation) The recom-

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

Pediatric Use: There is no experience with oral GRANISETRON in the prevention of radiation-induced nausea and vomiting in pediatric patients.
Use in the Elderly No dosage adjustment is recommended.

INSTRUCTIONS

Dosage as directed by the physician.
Store below 30°C. Protect from heat and light.
Tighten the cap securely after use. Keep all medicines out of the reach of children.
For Oral Use only. Do not use oral solution if seal is damaged or open.

PRESENTATION

Sitensa (Granisetron) Oral Solution is available in 30mL labeled Amber PET bottle in a carton with Spoon.

ہدایات:
خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
۳۰ ڈگری سینٹی گریڈ سے کم پر رکھیں۔روشنی اور گرمی سے محفوظ رکھیں۔
استعمال کے بعد ڈھکن کو اچھی طرح بند کرلیں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔
صرف پینے کے لئے استعمال کریں۔
اورل سلوشن کی سیل خراب یا کھلی ہونے کی صورت میں استعمال نہ کریں۔

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