Granisol Injection (Granisetron) 3mg/3ml

گرینیسول انجیکشن (گرینیسیٹرون) 3ملی گرام/3ملی لیٹر

COMPOSITION

Each 3ml contains:

Granisetron Hydrochloride eq. to Granisetron……..……3mg

(USP Specifications)

DESCRIPTION

Granisetron hydrochloride Injection is a serotonin-3 (5-HT3) 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). It is used to treat nausea and vomiting in cancer therapy and postoperatively.

INDICATIONS

Granisetron Injection is a serotonin-3 (5-HT3) 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.

• The prevention and treatment of postoperative nausea and vomiting in adults. As with other anti-emetics, routine prophylaxis is not recommended in patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and/or vomiting must be avoided during the postoperative period, Granisetron hydrochloride Injection is recommended even where the incidence of postoperative nausea and/or vomiting is low.

MECHANISM OF ACTION

Granisetron is a potent anti-emetic and highly selective antagonist of 5-hydroxytryptamine (5-HT3) receptors. Radioligand binding studies have demonstrated that granisetron has negligible affinity for other receptor types including 5-HT and dopamine D_2 binding sites.

DOSAGE & ADMINISTRATION

Prevention of Chemotherapy-Induced Nausea and Vomiting

Adult Patients

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

Infusion Preparation

Granisetron hydrochloride 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.

Stability

Intravenous infusion of granisetron hydrochloride injection should be prepared at the time of administration. However, granisetron hydrochloride 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, granisetron hydrochloride 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.

Pediatric Patients

The recommended dose in pediatric patients 2 to 16 years of age is 10 mcg/kg. Pediatric patients under 2 years of age have not been studied.

Prevention and Treatment of Postoperative Nausea and Vomiting

Adult Patients

The recommended dosage for prevention of postoperative nausea and vomiting is 1 mg of granisetron hydrochloride, undiluted, administered intravenously over 30 seconds, before induction of anesthesia or immediately before reversal of anesthesia. The recommended dosage for the treatment of nausea and/or vomiting after surgery is 1 mg of granisetron hydrochloride , undiluted, administered intravenously over 30 seconds.

PHARMACOKINETICS

Pharmacokinetics of the oral administration is linear up to 2.5-fold of the recommended dose in adults. It is clear from the extensive dose-finding programme that the antiemetic efficacy is not unequivocally correlated with either administered doses or plasma concentrations of granisetron.

A fourfold increase in the initial prophylactic dose of granisetron made no difference in terms of either the proportion of patient responding to treatment or in the duration of symptoms control.

Distribution

Granisetron is extensively distributed, with a mean volume of distribution of approximately 3L / kg. Plasma protein binding is approximately 65%.

Biotransformation

Granisetron is metabolized primarily in the liver by oxidation followed by conjugation. The major compounds are 7-OH-granisetron and its sulphate and glycuronide conjugates. Although antiemetic properties have been observed for 7-OH-granisetron and indazoline N-desmethyl granisetron, it is unlikely that these contribute significantly to the pharmacological activity of granisetron in man. 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.

Elimination

Clearance is predominantly by hepatic metabolism. Urinary excretion of unchanged granisetron averages 12% of dose while that of metabolites amounts to about 47% of dose. The remainder is excreted in faeces as metabolites. Mean plasma half-life in patients by the oral and intravenous route is approximately 9 hours, with a wide inter-subject variability.

WARNINGS & PRECAUTIONS

Gastric or Intestinal Peristalsis

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

Cardiovascular Events

An adequate QT assessment has not been conducted, but QT prolongation has been reported with Granisetron. Therefore, Granisetron 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.

Hypersensitivity Reactions

Hypersensitivity reactions (eg. anaphylaxis, shortness of breath, hypotension, urticaria) may occur in patients who have exhibited hypersensitivity to other selective 5-HT3 receptor antagonists.

Benzyl Alcohol

Granisetron 1 mg/mL contains benzyl alcohol. Benzyl alcohol, a component of Granisetron. 1 mg/mL, has been associated with serious adverse reactions and death, particularly in neonates. The “gasping syndrome,” characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and metabolites in blood and urine, has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low birth-weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping

syndrome," the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low birth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

Pregnancy

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. Benzyl alcohol may cross the placenta. Granisetron Injection 1 mg/mL is preserved with benzyl alcohol and should be used in pregnancy only if the benefit outweighs the potential risk.

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 Injection is administered to a nursing woman.

Pediatric Use

Benzyl alcohol, a component of Granisetron 1mg/mL, has been associated with serious adverse reactions and death, particularly in neonates.

SIDE EFFECTS

The most frequently reported adverse reactions for granisetron are headache and constipation which may be transient. ECG changes including QT prolongation have been reported with granisetron.

As with other 5-HT3 antagonists, cases of serotonin syndrome (including altered mental status, autonomic dysfunction and neuromuscular abnormalities) have been reported following the concomitant use of granisetron and other serotonergic drugs.

Hepatic: In comparative trials, mainly with cisplatin regimens, elevations of AST and ALT (>2 times the upper limit of normal) following administration of Granisetron 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 (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 Granisetron Injection (8.6%) than with comparative drugs (3.4%, P<0.014), which usually included dexamethasone.

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 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 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by Granisetron in vitro. 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. QT prolongation has been reported with Granisetron. Use of granisetron in patients concurrently treated with drugs known to prolong the QT interval and/or are arrhythmogenic may result in clinical consequences.

CONTRAINDICATIONS

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

OVERDOSE

There is no specific antidote for Granisetron 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.

STORAGE & INSTRUCTIONS

Store below 30°C.

Protect from heat, sunlight and moisture.

Keep away from the reach of the children.

Do not use the injection if any particulate matter is present, container is leaking or solution is cloudy.

To be sold on the prescription of a registered medical practitioner only.

For Intravenous use only.

HOW SUPPLIED

GRANISOL Injection 3mg/3ml

1 Ampoule

خوراک و ہدایات:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔ دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔ دھوپ، گرمی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔ صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔ صرف وریدی استعمال کے لیے ہے۔

Manufactured by:

PHARMASOL

PRIVATE LIMITED

Plot # 549,Sundar Industrial Estate,
Lahore, Pakistan.