Published on: 10 Jul 2014

GRANICIP Injection (Granisetron hydrochloride)

Composition

GRANICIP 3 mg Injection
Each ml contains:
Granisetron Hydrochloride, USP
equivalent to Granisetron ..... 1 mg
Water for Injection, IP ..... q.s.

Dosage Form

Injection

Pharmacology

Pharmacodynamics

Granisetron is a selective 5-hydroxytryptamine3 (5-HT3) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT1; 5-HT1A; 5-HT1B/C; 5-HT2; for alpha1-, alpha2- or beta-adrenoreceptors; for dopamine-D2; or for histamine-H1; benzodiazepine; and picrotoxin or opioid receptors.
Serotonin receptors of the 5-HT3-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-HT3-receptors. This evokes vagal afferent discharge and may induce vomiting. Animal studies demonstrate that, in binding to 5-HT3-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.

Pharmacokinetics

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 1.

Table 1: 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)	Total Clearance (L/h/kg)
Cancer Patients Mean range	63.8* 18.0 to 176	8.95* 0.90 to 31.1	0.38* 0.14 to 1.54	3.07* 0.85 to 10.4
Volunteers 21 to 42 years Mean range 65 to 81 years Mean range	64.3† 11.2 to 182 57.0† 14.6 to 153	4.91† 0.88 to 15.2 7.69† 2.65 to 17.7	0.79† 0.20 to 2.56 0.44† 0.17 to 1.06	3.04† 1.68 to 6.13 3.97† 1.75 to 7.01
* 5-minute infusion †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 (CY) P450 3A subfamily. Animal studies suggest that some of the metabolites may also have 5-HT3-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 faeces.

Subpopulations

Gender

There was high inter- and intra-subject variability noted in these studies. No difference in the 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 the half-life in the elderly patients (see Table 1).

Paediatric Patients

A pharmacokinetic study in paediatric 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 is similar in paediatric 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 the 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.

Indications

GRANICIP 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 (chemotherapy or radiotherapy), including high-dose cisplatin.

Dosage And Administration

GRANICIP Injection is for intravenous administration only.

Prevention of Chemotherapy-Induced Nausea and Vomiting

Adult Patients

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

Infusion Preparation

GRANICIP 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

The intravenous infusion of GRANICIP Injection should be prepared at the time of administration. However, GRANICIP Injection has been shown to be stable for at least 24 hours when diluted with 0.9% Sodium Chloride or 5% Dextrose and stored at room temperature under normal lighting conditions.

As a general precaution, GRANICIP Injection should not be mixed in a solution with other drugs. Parenteral drug products should be inspected visually for particulate matter and discolouration before administration whenever solution and container permit.

Paediatric Patients

The recommended dose in paediatric patients, 2 to 16 years of age, is 10 mcg/kg. Paediatric patients below 2 years of age have not been studied.

Maximum Daily Dose

The maximum dose of GRANICIP Injection to be administered over 24 hours should not exceed 9 mg.

Concomitant Use of Corticosteroids

The efficacy of GRANICIP Injection may be enhanced by the addition of dexamethasone (8-20 mg) or methylprednisolone (250 mg).

Contraindications

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

Warnings And Precautions

▶ Drug Interactions

Granisetron does not induce or inhibit the CYP450 drug-metabolizing enzyme system *in vitro*. There have been no definitive drug-drug interaction studies to examine the 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 anti-emetic treatments. Granisetron hydrochloride injection also does not appear to interact with emetogenic cancer chemotherapies. Because granisetron is metabolized by the hepatic CYP450 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 anaesthetized patients. In addition, the activity of the CYP450 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 the 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 the 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.

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.
Granisetron may reduce intestinal motility. Patients showing symptoms of sub-acute intestinal obstruction following administration of granisetron should be monitored carefully.

Cardiovascular Events

5-HT3 antagonists such as granisetron may be associated with arrhythmias or ECG abnormalities. 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 or patients who are being treated with anti-arrhythmic agents or beta-blockers, 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 (e.g. anaphylaxis, shortness of breath, hypotension, urticaria) may occur in patients who have exhibited hypersensitivity to other selective 5-HT3-receptor antagonists.

Renal Impairment

No special precautions are required for elderly patients or renally and/or hepatically impaired patients.

Hepatic Impairment

No special precautions are required for elderly patients or renally and/or hepatically impaired patients. Although, to date, no signs of an increased incidence of adverse events have been observed in hepatically impaired patients, owing to the

kinetics, a degree of caution should be exercised in using granisetron with this category.

Pregnancy

Whilst animal studies have shown no teratogenic effects, there is no experience of granisetron in human pregnancy. Therefore, granisetron should not be administered to women who are pregnant unless there are compelling clinical reasons.

Lactation

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 mother.

Paediatric Use

Safety and effectiveness in paediatric patients below 2 years of age have not been established.

Geriatric Use

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

Undesirable Effects

The most frequent adverse effect is headache, occurring in about 14% of patients. Other less common adverse events associated with granisetron administration include hypersensitivity reactions (e.g. anaphylaxis), constipation, diarrhoea, asthenia and somnolence.
The frequency of side effects is classified into the following categories:

Very common	≥1/10
Common	≥1/100, <1/10
Uncommon	≥1/1000, <1/100
Rare	≥1/10 000, <1/1000
Very rare	<1/10 000, not known (cannot be estimated from the available data)

Incidence and severity are as given below:

Cardiac disorders	Rare: Arrhythmias such as sinus bradycardia, atrial fibrillation, varying degrees of AV-block, ventricular ectopy (including non-sustained tachycardia), ECG abnormalities Uncommon: QT interval prolonged
Nervous system disorders	Very common: Headache Common: Somnolence, agitation, anxiety, central nervous system (CNS) stimulation and insomnia, taste disorder Rare: Dystonia and dyskinesia have been reported with medicines in the 5-HT3 antagonist class , as also extrapyramidal syndromes Uncommon: Extrapyramidal reactions
Eye disorders	Uncommon: Abnormal vision
Ear and labyrinth disorders	Common: Dizziness

Gastrointestinal disorders	Very common: constipation Common: Diarrhoea, anorexia
Skin and subcutaneous tissue disorders	Uncommon: Skin rashes Rare: Local irritation at the administration site after repeated intravenous administration
Vascular disorders	Common: Hypertension Rare: Hypotension
General disorders	Common: Fever, asthenia
Immune system disorders	Rare: Hypersensitivity reactions, sometimes severe (e.g. anaphylaxis, shortness of breath, hypotension, urticaria) Very Rare: Oedema (including facial oedema)
Hepatobiliary disorders	Rare: Abnormal hepatic function, raised transaminase levels Common: Elevations of AST and ALT (>2 times the upper limit of normal)

▶ Postmarketing Experience

QT prolongation has been reported with granisetron hydrochloride.

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.

Shelf-Life

3 years

Storage And Handling Instructions

Once the multi-use vial is opened, its contents should be used within 30 days.
Do not freeze. Protect from light. Retain in the carton until the time of use.

Packaging Information

GRANICIP Injection: Vial of 5 ml
Last updated: December 2013
Last reviewed: December 2013

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