PACKAGE INSERT TEMPLATE FOR GRANISETRON TABLET & AMPOULE FOR INTRAVENOUS INJECTION/INFUSION

Brand or Product Name
[Product name] Tablet 1mg
[Product name] Ampoule 3mg/3ml
[Product name] Ampoule 1mg/ml

Name and Strength of Active Substance(s)
Granisetron hydrochloride …mg equivalent to …mg granisetron

Product Description
[Visual description of the appearance of the product (eg colour, markings etc)]
eg An ampoule containing a sterile, clear, colourless or slightly straw-coloured solution
White, circular flat beveled edge tablets marked '1' on one side

Pharmacodynamics

Granisetron hydrochloride is a selective antagonist of 5-hydroxytryptamine (3) (5-HT(3)) receptors present peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone. Binding results in blockade of serotonin stimulation and subsequent vomiting triggered by emetogenic stimuli. Granisetron hydrochloride has little or no affinity for other serotonin receptors, for adrenergic, for dopamine-D (2), histamine-H (1), benzodiazepine, picrotoxin or opioid receptors.

Pharmacokinetics

Absorption
Granisetron is rapidly absorbed after oral doses and peak plasma concentrations occur after about 2 hours. Oral bioavailability is about 60% as a result of first-pass hepatic metabolism.
Oral bioavailability is generally not influenced by food.

Distribution
Granisetron has a large volume of distribution of around 3 litres/kg
The protein binding of granisetron is 65%
Granisetron distributes freely between plasma and red blood cells
Granisetron is widely distributed in body tissues
Volume of Distribution 0.8 to 10.4 L/kg

Metabolism
Metabolism involves N-demethylation and aromatic ring oxidation followed by conjugation.
Metabolism is most likely mediated by the cytochrome P-450 3A subfamily.

Granisetron appears to be metabolized in the liver.
Approximately 11% of the orally dose is eliminated unchanged in the urine within 48 hours.
The remainder of the dose is excreted as metabolites, 48% in the urine and 38% in the feces
Metabolites may have 5-HT3 receptor antagonist activity

Excretion
Granisetron clearance is not affected by renal impairment, but is lower in the elderly and in patients with hepatic impairment.

Renal Excretion: Approximately 12% of an intravenous dose and 11% of the oral dose is eliminated unchanged in the urine over 48 hours
Feces: Approximately 83% to 86% of the dose is excreted as metabolites. Of this amount that is excreted as metabolites, 38% of the oral dose and 34% of the IV dose are eliminated in the feces

Indication
Granisetron is indicated for the prevention and treatment (control) of

a) acute and delayed nausea and vomiting associated with chemotherapy and radiotherapy

b) post-operative nausea and vomiting

Recommended Dosage

Chemotherapy Induced Nausea and Vomiting (CINV)

Adults

Oral Tablets:

Prevention: 1 mg twice a day or 2 mg once a day for up to one week following chemotherapy. The first dose of Granisetron should be administered within 1 hour before the start of therapy.

Intravenous:

Prevention: A dose of 1-3 mg (10-40mcg/kg) of Granisetron should be administered either as a slow intravenous injection (over 30 seconds) or as an intravenous infusion diluted in 20 to 50 ml infusion fluid and administered over 5 minutes, prior to the start of chemotherapy.

Treatment: A dose of 1-3 mg (10-40mcg/kg) Granisetron should be administered either as a slow intravenous injection (over 30 seconds) or as an intravenous infusion diluted in 20 to 50 ml infusion fluid and administered over 5 minutes. Further treatment doses of Granisetron may be administered, if required, at least 10 minutes apart. The maximum dose of Granisetron to be administered over 24 hours should not exceed 9 mg.

Intramuscular:

Prevention and Treatment: A dose of 3 mg of Granisetron should be administered by the intramuscular route, 15 minutes prior to the start of chemotherapy. Two subsequent 3 mg doses of Granisetron may be administered, if required, within a 24 hour period.

Paediatrics

Intravenous:

A dose of 10-40 mcg/kg body weight (up to 3 mg) should be administered as an intravenous infusion, diluted in 10 to 30 ml infusion fluid and administered over 5 minutes prior to the start of chemotherapy. One additional dose may be administered within a 24 hour period if required. This additional dose should not be administered until at least 10 minutes after the initial infusion.

Intramuscular: Insufficient data are currently available to recommend the use of Granisetron by the intramuscular route in children.

Radiotherapy Induced Nausea and Vomiting (RINV)

Adults

Oral Tablets: 2 mg once a day for up to one week following radiotherapy. The first dose of GRANISETRON should be administered within 1 hour before the start of therapy.

Intravenous:

Prevention: A dose of 1-3 mg (10-40mcg/kg) of Granisetron should be administered either as a slow intravenous injection (over 30 seconds) or as an intravenous infusion diluted in 20 to 50 ml infusion fluid and administered over 5 minutes, prior to the start of radiotherapy.

Paediatrics

There is insufficient information to recommend use of Granisetron in the prevention and treatment of RINV in children.

Post-operative Nausea and Vomiting (PONV)

Adults

Intravenous

Prevention: A dose of 1 mg (10mcg/kg) of Granisetron should be administered as a slow intravenous injection (over 30 seconds) prior to induction of anesthesia.

Treatment: A dose of 1 mg (10mcg/kg) of Granisetron should be administered by slow intravenous injection (over 30 seconds). The maximum dose for patients undergoing anesthesia for surgery is a total dose of 3 mg of Granisetron i.v. in one day.

Paediatrics

There is insufficient information to recommend use of Granisetron in the prevention and treatment of postoperative nausea and vomiting in children.

Special Dosage Instructions

Geriatrics: No dosage adjustments required.

Renal impairment: No dosage adjustments required.

Hepatic Impairment: No dosage adjustments required.

Mode of Administration
Oral
Intravenous
Intramuscular

Contraindications
Contraindicated in patients hypersensitive to granisetron or its excipients

Warnings and Precautions
As Granisetron may reduce lower bowel motility, patients with signs of sub-acute intestinal obstruction should be monitored closely following administration of Granisetron.

As for other 5-HT3 antagonists, cases of ECG modifications including QT prolongation have been reported with granisetron. These ECG changes with granisetron were minor and generally not of clinical significance, specifically with no evidence of proarrhythmia. However, in patients with pre-existing arrhythmias or cardiac conduction disorders, this might lead to clinical consequences. Therefore, caution should be exercised in patients with cardiac co-morbidities, on cardio-toxic chemotherapy and/or with concomitant electrolyte abnormalities.

Granisetron multi-dose vials contain benzyl alcohol. Benzyl alcohol should not be used in infants less than 3 months of age (if applicable).

Effects on ability to drive and use machines

There has been no evidence from human studies that granisetron has any adverse effect on alertness.

Interactions with Other Medicaments

The metabolism of granisetron is induced by phenobarbital.

Granisetron has been safely administered in humans with benzodiazepines, neuroleptics and anti-ulcer medications, commonly prescribed with antiemetic treatments.

Granisetron has shown no apparent drug interaction with emetogenic cancer chemotherapies.

Granisetron has been safely administered with commonly used anesthetic and analgesic agents.

In patients concurrently treated with drugs known to prolong QT interval and/or are arrhythmogenic, this may lead to clinical consequences.

Statement on Usage During Pregnancy and Lactation

Pregnancy

No human studies have been conducted on the use of granisetron during pregnancy. Due to the lack of human reproductive studies, granisetron should be used during pregnancy only if clearly needed

Lactation

Infant risk cannot be ruled out. Available evidence and/or expert consensus are inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

Adverse Effects / Undesirable Effects

- Neurologic: asthenia , headache ,somnolence
- Cardiovascular: prolonged QT interval
- Immunologic: hypersensitivity reaction(rashes and anaphylaxis)
- Other: fever , constipation, elevations in hepatic transaminases

Overdose and Treatment

There is no specific antidote for Granisetron. In the case of over dosage with granisetron, symptomatic treatment should be given.

Incompatibilities

[To add appropriate information based on formulation]

Instructions for Use, Handling and Disposal
[To add appropriate information and graphic]

Storage Conditions
[eg Store below….°C]

Dosage Forms and Packaging Available
[Packaging type & pack size]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]