FRESENIUS KABI

GRANISETRON FRESENIUS 1mg/mL

Injection

COMPOSITION
Each mL contains:
Granisetron HCl equivalent to 1 mg of Granisetron.

LIST OF EXCIPIENTS
Sodium Chloride, Citric Acid Monohydrate, Sodium Hydroxide, Hydrochloric Acid, and Water for Injection.

PHARMACOLOGY
Serotonin receptors of the 5-HT_3 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-HT_3 receptors. This evokes vagal afferent discharge and may induce vomiting. Granisetron is a highly selective antagonist of 5-hydroxytryptamine (5-HT_3) receptors and displays potent antiemetic activity.

PHARMACOKINETICS
Absorption
Absorption of Granisetron is generally not influenced by food and is rapid and complete, though oral bioavailability is reduced to around 60% as a result of first pass metabolism.
Distribution
Granisetron is widely distributed with a mean volume of distribution of approximately 3 liters/kg; plasma protein binding is approximately 65%.
Metabolism
Biotransformation pathways involve N-demethylation and aromatic ring oxidation followed by conjugation.
Elimination
Clearance is predominantly by hepatic metabolism. Urinary excretion of unchanged Granisetron averages 12% of dose whilst that of metabolites amounts to about 47% of dose. The remainder is excreted in feces as metabolites. Mean plasma half-life in patients is approximately nine hours, with a wide inter-subject variability.

INDICATIONS
Granisetron is indicated for the prevention or treatment of nausea and vomiting induced by cytostatic therapy and for the prevention and treatment of post-operative nausea and vomitting.

DOSAGE AND ADMINISTERING PROCEDURE
Cytostatic therapy
Intravenous
Granisetron ampoules are for intravenous administration only.

Adults
3 mg Granisetron which should be administered either in 15 mL infusion fluid as an intravenous bolus over not less than 30 seconds or diluted in 20 to 50 mL infusion fluid and administered over five minutes.

Prevention: in clinical trials, the majority of patients have required only a single dose of Granisetron to control nausea and vomiting over 24 hours. Up to two additional doses of 3 mg Granisetron may be administered within a 24-hour period. There is clinical experience in patients receiving daily administration for up to five consecutive days in one course of therapy. Prophylactic administration of Granisetron should be completed prior to the start of cytostatic therapy.

Treatment: the same dose of Granisetron should be used for treatment as prevention. Additional doses should be administered at least 10 minutes apart.

Maximum daily dosage: up to three doses of 3 mg Granisetron may be administered within a 24-hour period. The maximum dose of Granisetron to be administered over 24 hours should not exceed 9 mg.

Concomitant use of dexamethasone
The efficacy of Granisetron may be enhanced by the addition of dexamethasone.

Elderly
No special requirements apply to elderly patients.

Children
Prevention: a single dose of 40 micrograms/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 five minutes. Administration should be completed prior to the start of cytostatic therapy.

Treatment: the same dose of Granisetron as above should be used for treatment as prevention.
One additional dose of 40 micrograms/kg body weight (up to 3 mg) may be administered within a 24-hour period. This additional dose should be administered at least 10 minutes apart from the initial infusion.

Patients with renal or hepatic impairment
No special requirements apply to those patients with renal or hepatic impairment.

Administration
Adults
To prepare a dose of 3 mg, 3 mL is withdrawn from the ampoule and diluted either to 15 mL with NaCl 0.9% infusion solution or in infusion fluid to a total volume of 20 to 50 mL in any of the following solutions: NaCl 0.9% infusion solution, Dextrose 5% infusion solution and Ringer Lactate infusion solution. No other diluents should be used.

Children
To prepare the dose of 40 micrograms/kg the appropriate volume (up to 1 mL from the 1mg ampoule or up to 3 mL from the 3 mg ampoule) is withdrawn and diluted with infusion fluid (as for adults) to a total volume of 10 to 30 mL.

Post-operative nausea and vomiting
Intravenous

Adults
Prevention: for prevention in adults, a single dose of 1 mg of Granisetron should be diluted to 5 mL and administered as a slow intravenous injection (over 30 seconds). Administration should be completed prior to induction of anesthesia.

Treatment: for the treatment of established post-operative nausea and vomiting in adults, a single dose of 1 mg of Granisetron should be diluted to 5ml and administered by slow intravenous injection (over 30 seconds).

Maximum dose and duration of treatment: two doses (2 mg) in one day.

Administration
Adults
To prepare a dose of 1 mg, 1 mL should be withdrawn from the ampoule and diluted to 5ml with NaCl 0.9% infusion solution. No other diluents should be used.

Children
There is no experience in the use of Granisetron in the prevention and treatment of post-operative nausea and vomiting in children. Granisetron is not therefore recommended for the treatment of post-operative nausea and vomiting in this age group.

Elderly patients
As for adults.

Renally impaired and hepatically impaired patients
As for adults.

CONTRAINDICATION
Known hypersensitivity to Granisetron or any of the excipients.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
As Granisetron may reduce lower bowel motility, patients with signs of subacute intestinal obstruction should be monitored following administration of Granisetron.
As with other 5-HT_3 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 comorbidities, on cardiotoxic chemotherapy and/or with concomitant electrolyte abnormalities.
Cross-sensitivity between 5-HT_3 antagonists has been reported. Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take this medicine.

As with other 5-HT_3 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. If concomitant treatment with granisetron and other serotonergic drugs is clinically warranted, appropriate observation of this patient is advised.
There has been no evidence from human studies that Granisetron has any adverse effect on alertness.
As a general precaution, Granisetron should not be mixed in solution with other drugs. Prophylactic administration of Granisetron should be completed prior to the start of cytostatic therapy or induction of anesthesia.
Data from two-year carcinogenicity studies have shown an increase in hepatocellular carcinoma and/or adenoma in rats and mice of both sexes given 50 mg/kg (rat dosage reduced to 25 mg/kg/day at week 59). Increases in hepatocellular neoplasia were also detected at 5mg/kg in male rats. In both species, drug-induced effects (hepatocellular neoplasia) were not observed in the low-dose group (1 mg/kg). In several in vitro and in vivo assays, Granisetron was shown to be nongenotoxic in mammalian cells.

PREGNANCY AND BREASTFEEDING
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. There are no data on the excretion of Granisetron in breast milk. Breast-feeding should therefore be discontinued during therapy.

EFFECTS ON DRIVING AND MACHINE OPERATING ABILITY
Granisetron has no negligible influence on the ability to drive or to use machine.

DRUG INTERACTION
In studies in healthy subjects, no evidence of any interaction has been indicated between Granisetron and cimetidine or lorazepam. No evidence of drug interactions has been observed in clinical studies conducted.
No specific interaction studies have been conducted in anesthetized patients, but Granisetron has been safely administered with commonly used anesthetic and analgesic agents. In addition, in vitro human microsomal studies have shown that the cytochrome P450 subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by Granisetron.
As for other 5-HT_3 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 concurrently treated with drugs known to prolong QT interval and/or are arrhythmogenic, this may lead to clinical consequences.
As with other 5-HT_3 antagonists, cases of serotonin syndrome have been reported following the concomitant use of Granisetron and other serotonergic drugs. If concomitant treatment with granisetron and other serotonergic drugs is clinically warranted, appropriate observation of this patient is advised.

ADVERSE REACTION
Summary of the safety profile
The most frequently reported adverse reactions for Granisetron are headache and constipation which may be transient. ECG changes include QT prolongation have been reported with Granisetron.
The following table of listed adverse reactions is derived from clinical trials and post-marketing data associated with Granisetron.

Frequency categories are as follows:
Very common : ≥1/10;
Common : ≥1/100 to < 1/10;
Uncommon : ≥1/1,000 to < 1/100;
Rare : ≥1/10,000 to < 1/1,000;
Very rare : < 1/10,000

Table 1 Tabulated List of Adverse Reactions

Immune system disorders	
Uncommon	Hypersensitive reactions e.g. anaphylaxis, urticaria
Nervous system disorders	
Very common	Headache
Uncommon	Serotonin Syndrome
Cardiac disorders	
Uncommon	QT prolongation
Gastrointestinal disorders	
Very common	Constipation
Hepatobiliary disorders	
Common	Elevated hepatic transaminases*
Skin and subcutaneous tissue disorders	
Uncommon	Rash

*Occurred at a similar frequency in patients receiving comparator therapy

Granisetron has been generally well-tolerated in human studies. As reported with other drugs of this class, headache and constipation have been the most frequently noted adverse events, but the majority have been mild or moderate in nature. Cases of hypersensitivity reaction, occasionally severe (e.g. anaphylaxis) have been reported. Other allergic reactions including minor skin rashes have also been reported. In clinical trials transient increases in hepatic transaminases, generally within the normal range, have been seen.
As for other 5-HT_3 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. (See **Special Warnings and Precautions for Use**, and **Drug Interaction**).
As with other 5-HT_3 antagonists, cases of serotonin syndrome (including altered mental status, automonic dysfunction and neuromuscular abnormalities) have been reported following the concomitant use of Granisetron and other serotonergic drugs.

OVERDOSE
There is no specific antidote for Granisetron. In the case of overdose with the injection or infusion, symptomatic treatment should be given. Doses of up to 30 mg of Granisetron as a single injection have been reported, with symptoms of mild headache but no other reported sequelae.

INSTRUCTION FOR USE AND HANDLING
Intravenous Injection Preparation

Granisetron HCl can be diluted with 0.9% Sodium Chloride Solution or 5% Dextrose Solution or Lactate Ringer infusion. Solution is stable for 24 hours when it is stored at 25°C.

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution/dilution etc has taken place in controlled and validated aseptic conditions.

PACKING
Box, 5 ampoules @ 1 mL
Box, 5 ampoules @ 3 mL
Reg. No.

Manufactured and Batch Released by:
PT. ETHICA Industri Farmasi
Bekasi - Indonesia
Kawasan Industri Jababeka Tahap V, Blok B1B1,
Desa Jayamukti, Kecamatan Cikarang Pusat,
Kabupaten Bekasi, Jawa Barat - Indonesia

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