NAME OF THE MEDICINE
GRANISETRON KABI
Granisetron hydrochloride concentrated Injection

PRESENTATION
Granisetron is administered as the hydrochloride salt, granisetron hydrochloride.

Granisetron Kabi Concentrated Injection solution contains a clear colourless solution equivalent to 1 mg of granisetron per 1 mL. Granisetron Kabi is available in 1 mL ampoules containing granisetron 1 mg/1 mL; and 3 mL ampoules containing granisetron 3 mg/3 mL.

USES
Actions
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 D2 binding sites.

Granisetron is effective intravenously (either prophylactically or by intervention), in abolishing the retching and vomiting evoked by administration of cytotoxic drugs or by whole body X-irradiation.

Granisetron is effective, intravenously, in the prevention and treatment of post-operative nausea and vomiting.

Granisetron did not affect the plasma levels of prolactin or aldosterone.

PHARMACOKINETICS
Absorption
Absorption of granisetron is rapid and complete.

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

Biotransformation
Biotransformation pathways involve N-demethylation and aromatic ring oxidation followed by conjugation.

Elimination
Clearance is predominantly via 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 faeces as
metabolites. Mean plasma half-life is approximately 9 hours, with a wide inter-subject variability.

The pharmacokinetics of intravenous granisetron demonstrate no marked deviations from linear pharmacokinetics at intravenous doses up to 4-fold the recommended clinical dose.

The results of a study in healthy male volunteers have demonstrated that systemic delivery of 3 mg granisetron from an intramuscular injection is slower than from a 5 minute intravenous infusion (as indicated by lower C_{\text{max}} and later T_{\text{max}}).

In other respects, the pharmacokinetics of granisetron are virtually indistinguishable when administered by these two different routes.

**Characteristics in patients**
The plasma concentration of granisetron is not clearly correlated with anti-emetic efficacy. Clinical benefit may be conferred even when granisetron is not detectable in plasma.

In elderly subjects after single intravenous doses, pharmacokinetic parameters were within the range found for non-elderly subjects.

In patients with severe renal failure, data indicate that pharmacokinetic parameters after a single intravenous dose are generally similar to those in normal subjects.

In patients with hepatic impairment due to neoplastic liver involvement, total clearance of an intravenous dose was approximately halved compared to patients without hepatic impairment. Despite these changes, no dose adjustment is necessary.

In children, after single intravenous doses, pharmacokinetics are similar to those in adults when appropriate measures (volume of distribution, total plasma clearance) are normalised for bodyweight.

**INDICATIONS**
Granisetron is an antiemetic.

Granisetron is indicated for the prevention of acute and delayed nausea and vomiting associated with cytostatic therapy, and for the prevention and treatment of postoperative nausea and vomiting.

**DOSAGE AND ADMINISTRATION**

**Cytostatic Therapy (dose in adults)**
The recommended intravenous dose of granisetron is 3 mg. The dose should be administered no more than 30 minutes before the start of cytostatic therapy.
Granisetron should be administered by intravenous infusion. The dose should be diluted to a total volume of 20 mL to 50 mL in compatible infusion fluid and administered over 5 minutes. To prepare an infusion, withdraw a total of 3 mL from the ampoule and dilute in 0.9% sodium chloride of 5% dextrose, (see Pharmaceutical Precautions).

In clinical trials, the majority of patients have required only a single dose of granisetron to control nausea and vomiting over 24 hours. In the small proportion of patients with breakthrough nausea and vomiting, up to two additional 5-minute infusions of 3 mg of granisetron, given at least 10 minutes apart, may be administered within a 24-hour period. The maximum dose of granisetron is 9 mg/24 hours.

In trials, patients have received a total dose of 160 µg/kg of intravenous granisetron in one day. There is also clinical experience in patients receiving a total of 600 µg/kg of intravenous granisetron over 5 days.

Cytostatic Therapy (dose in children)
The recommended intravenous dose of granisetron is 20 mcg/kg body weight, which should be administered no more than 30 minutes before the start of cytostatic therapy. In patients with breakthrough nausea and vomiting, up to two additional doses of 20 mcg/kg, given at least 10 minutes apart, may be administered within a 24 hour period.

Granisetron should be administered by intravenous infusion. The dose should be diluted to a total volume of 10 mL to 30 mL in compatible infusion fluid and administered over 5 minutes. To prepare the infusion, withdraw the appropriate volume and dilute in 0.9% sodium chloride of 5% dextrose, (see Pharmaceutical Precautions).

During clinical trials in paediatric patient, some patients received up to a total of 80 mcg/kg/day.

Post-operative Nausea and Vomiting (dose in adults)
For prevention of post-operative nausea and vomiting in adults, a single dose of 1 mg of granisetron should be administered as a slow 30 second intravenous injection prior to induction of anaesthesia.

For the treatment of established post-operative nausea and vomiting in adults, a single dose of 1 mg of granisetron should be administered by slow intravenous injections, over 30 seconds.

Patients undergoing anaesthesia for elective surgery have received a total dose of 3 mg granisetron intravenous in one day.

Post-operative Nausea and Vomiting (dose in children)
There is no experience in the use of granisetron in the prevention of post-operative nausea and vomiting in children.
Post-operative Nausea and Vomiting (dose in elderly)
As for adults

Post-operative Nausea and Vomiting (dose in renally or hepatically impaired)
As for adults

CONTRAINDICATIONS
Granisetron is contraindicated in patients hypersensitive to granisetron and 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.

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

Use in Pregnancy and Lactation
In the rat, granisetron had no untoward effect on reproductive performance, fertility or on pre- and post-natal development. Teratogenic effects were not observed in rats or rabbits. As there is no experience with the use of granisetron during human pregnancy or lactation, its use should be limited to situations where the potential benefit to the mother justifies the potential risk to the foetus or nursing infant.

Effects on the Ability to Drive and Use Machines
In healthy subjects, no clinically relevant effects on resting EEG or on the performance of psychometric tests were observed after i.v. granisetron at any dose tested (up to 200 mcg/kg).

ADVERSE EFFECTS
Granisetron has been well tolerated in human studies. In common with other drugs of this class, headache and constipation have been reported. These were generally mild or moderate in nature and tolerated by patients. Rare cases of hypersensitivity reaction, occasionally severe (e.g. anaphylaxis) have been reported. Other allergic reactions including minor skin rashes have also been reported. Transient rises in hepatic transaminases have been observed rarely and at similar frequency in patients receiving comparator therapy.

INTERACTIONS
Granisetron does not induce or inhibit the cytochrome P450 drug metabolising enzyme system in rodent studies or inhibit the activity of any well characterised P450 subfamilies studies in in vitro investigations. In humans, hepatic enzyme induction with phenobarbital resulted in an increase in total plasma clearance of intravenous granisetron of approximately one-quarter. In in vitro human microsomal studies, ketoconazole inhibited ring oxidation of granisetron.
However, given the absence of pK/pD relationship with granisetron, these changes are believed to have no clinical consequences.

Granisetron has been safely administered in humans with benzodiazepines, neuroleptics, and anti-ulcer medications commonly prescribed with anti-emetic treatments. Additionally, granisetron has shown no apparent drug interaction with emetogenic cancer chemotherapies.

No specific interaction studies have been conducted in anaesthetised patients, but granisetron injections have been safely administered with commonly used anaesthetic and analgesic agents. In addition, the activity of the cytochrome P450 subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by granisetron.

**OVERDOSAGE**

In the case of overdosage with granisetron, symptomatic treatment should be given. Overdosage of up to 38.5 mg of granisetron hydrochloride as a single injection has been reported without symptoms or only the occurrence of a slight headache. There is no specific antidote for Granisetron Kabi.

**PHARMACEUTICAL PRECAUTIONS**

**Shelf Life and Special Precautions for Storage**
Granisetron Kabi concentrated injection solution ampoules should be stored at or below 25°C and protected from direct sunlight. Do not freeze. Single-use only.

Granisetron Kabi has been shown to be stable for at least 24 hours in the cited solutions (see Dosage and Administration) when stored at ambient temperature (15 to 25°C) in normal indoor illumination (natural daylight supplemented by fluorescent light). In order to reduce microbiological hazards, it is recommended that the infusion be commenced as soon as practicable after its preparation, and should be completed within 24 hours.

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

Discard any unused portion after opening.

**Medicine Classification**
Prescription Only Medicine

**Package Quantities**
Granisetron Kabi is available in packs of 1, 5 and 10 clear glass ampoules in the following presentations:

Granisetron Kabi 1 mg/1 mL
Granisetron Kabi 3 mg/3 mL

**FURTHER INFORMATION**

**Preclinical Safety Data**
Granisetron was not mutagenic in mammalian or non-mammalian *in vivo or in vitro* test systems and there was no evidence of unscheduled DNA synthesis indicating that granisetron is not genotoxic.

At higher doses, granisetron induced cell proliferation in the rat liver and hepatocellular tumours in rats and mice that were treated orally for their lifetime (2 years). Hepatocellular tumours were not observed in 2-year rodent studies at dosages 25 times the intravenous clinical dose.

In conclusion, granisetron was given without harm to rats and dogs for 12 months, at substantial multiples of the clinical dose. The finding of an increase in hepatocellular tumours at high doses in rodents, given drug for their lifetimes, is not considered to represent a hazard for the safe short-term use of granisetron as an antiemetic in humans.

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