Vaxcel®

GRANISETRON 1mg/ml

INJECTION PREFILLED SYRINGE

MAL

COMPOSITION:
Each ml contains
Granisetron Hydrochloride
equivalent to Granisetron
1mg

Benzyl Alcohol 1.0%w/v as preservative.

PRESENTATION:
Clear solution.

INDICATIONS:
Granisetron is indicated for the prevention and treatment of:
- Acute and delayed nausea and vomiting associated with chemotherapy and radiotherapy.
- Post-operative nausea and vomiting

PHARMACOLOGY:
Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin ($5\text{-}HT_3$) antagonists.
ATC code: A04AA02

Mechanism of Action:
Serotonin is the main neurotransmitter responsible for emesis after chemo- or radiotherapy. Serotonin receptors of the $5\text{-}HT_3$ type are located peripherally in 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 $5\text{-}HT_3$ receptors. This invokes vagal afferent discharge, inducing vomiting. Granisetron is a potent antiemetic and highly selective antagonist of 5-hydroxytryptamine ($5\text{-}HT_3$) receptors. Radioligand binding studies have demonstrated that Granisetron has negligible affinity for other receptor types including 5-HT and dopamine D_2 binding sites.

Chemotherapy - and radiotherapy-induced nausea and vomiting
Granisetron administered intravenously has been shown to prevent nausea and vomiting associated with cancer chemotherapy in adults and children 2 - 16 years of age.

Post-operative nausea and vomiting
Granisetron administered intravenously has been shown to be effective for prevention and treatment of post-operative nausea and vomiting in adults. Efficacy in children has not been established in controlled clinical trials.

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%.

Metabolism:
Biotransformation pathways involve 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 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 feces as metabolites. Mean plasma half-life in patients by the intravenous route is approximately 9 hours, with a wide inter-subject variability. The pharmacokinetics of intravenous granisetron demonstrate no marked deviations from linear pharmacokinetics at oral doses up to 2.5-fold and 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 3mg granisetron from an intramuscular injection is slower than from a 5 minute intravenous infusion (as indicated by lower Cmax and later Tmax). In other respects, the pharmacokinetics of granisetron are virtually indistinguishable when administered by these two different routes.

Special Populations:
Renal failure
Data indicate that pharmacokinetic parameters in patients with severe renal failure after a single intravenous dose are generally similar to those in normal subjects.

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

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

Pediatrics
After single intravenous doses, pharmacokinetics in children are similar to those in adults when appropriate parameters (volume of distribution, total plasma clearance) are normalized for body weight.

DOSAGE AND ADMINISTRATION:
Standard Dosage:
Chemotherapy Induced Nausea and Vomiting (CINV)
Adults:
Prevention: A dose of 1-3mg (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 50ml infusion fluid and administered over 5 minutes, prior to the start of chemotherapy.

Treatment: A dose of 1-3mg (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 50ml 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.

Pediatrics:
Prevention and treatment: A dose of 10-40mcg/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.

Radiotherapy Induced Nausea and Vomiting (RINV)
Adults:
Prevention: A dose of 1-3mg (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 50ml infusion fluid and administered over 5 minutes, prior to the start of radiotherapy.

Treatment: There is insufficient information to recommend the intravenous administration of granisetron in the treatment of RINV in adult patients.

Pediatrics:
There is insufficient information to recommend intravenous administration of granisetron in the prevention and treatment of RINV in children.

Post-operative Nausea and Vomiting (PONV)
Adults:
Prevention: A dose of 1mg (10mcg/kg) of granisetron should be administered as a slow intravenous injection (over 30 seconds) prior to induction of anesthesia.

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

Pediatrics:
There is insufficient information to recommend intravenous administration of granisetron in the prevention and treatment of postoperative nausea and vomiting in pediatric patients.

Special Dosage Instructions:
Geriatrics: No dosage adjustments required.
Renal impairment: No dosage adjustments required.
Hepatic impairment: No dosage adjustments required.

Method of administration:
Administration may be as either a slow intravenous injection (over 30 seconds) or as an intravenous infusion diluted in 20 - 50ml infusion fluid and administered over 5 minutes. The solution is clear after dilution.

Preparation of infusion:
For adults: The appropriate dose can be diluted with infusion fluid, to a total volume of 20 to 50ml in any of the following compatible solutions, and stable for up to 24 hours at room temperature (25±2°C), beyond that any unused solution should be discarded:
- 0.9% sodium chloride injection
- 0.18% sodium chloride + 4% dextrose
- 5% dextrose
- Hartmann's solution
- Sodium lactate
- Mannitol

For children: The appropriate dose is diluted with infusion fluid (as for adults) to a total volume of 10 to 30ml.

Special Remarks:
Admixtures of granisetron hydrochloride and dexamethasone sodium phosphate are compatible at concentrations of 10 to 60µg/ml granisetron and 80 to 480µg/ml dexamethasone sodium phosphate in either 0.9% sodium chloride or 5% glucose intravenous infusion fluids. The admixture will be stable for 24 hours.

ROUTE OF ADMINISTRATION:
For intravenous injection & infusion.

CONTRAINDICATION:
Contraindicated in patients hypersensitive to granisetron or any of its ingredients.

PRECAUTIONS:
As granisetron may reduce lower bowel motility, patients with signs of sub-acute intestinal obstruction should be monitored closely following its administration. As for other $5\text{-}HT_3$ antagonists, cases of Electrocardiogram (ECG) modifications including QT interval 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, this might lead to clinical consequences in patients with pre-existing arrhythmias or cardiac conduction disorders. Therefore caution should be exercised in patients with cardiac co-morbidities, on cardiotoxic chemotherapy and/or with concomitant electrolyte abnormalities. Cross-sensitivity between $5\text{-}HT_3$ antagonists (e.g. dolasetron, ondansetron) has been reported. As this preparation contains Benzyl Alcohol, its use should be avoided in children under two years of age. Not to be used in neonates.

SIDE EFFECTS:
Granisetron has been well tolerated in human studies. In common with other drugs of this class, headache and constipation have been reported. Rare cases of hypersensitivity reactions, including rashes and anaphylaxis have been reported. Elevations in hepatic transaminases have been observed and at similar frequency in patients receiving comparator therapy. As for other $5\text{-}HT_3$ 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.

DRUG INTERACTIONS:
Granisetron did not induce or inhibit the cytochrome P450 drug metabolizing enzyme system in rodent studies or inhibit the activity of any well characterized P450 sub-families studied in in vitro investigations. In humans, hepatic enzyme induction with phenobarbital resulted in an increase in total plasma clearance of intravenous granisetron of approximately 25%. Ketoconazole inhibited ring oxidation of granisetron in in vitro human microsomal studies. 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 antiemetic treatments. Additionally, granisetron has shown no apparent drug interaction with emetogenic cancer chemotherapies. 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, 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. As for other $5\text{-}HT_3$ 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 which are arrhythmogenic, this may lead to clinical consequences.

Incompatibilities:
Admixtures of granisetron hydrochloride and dexamethasone sodium phosphate are compatible at concentrations of 10 to 60µg/ml granisetron and 80 to 480µg/ml dexamethasone phosphate in either 0.9% sodium chloride or 5% glucose intravenous infusion fluids.

Pregnancy and lactation:
There are no studies in pregnant women and it is not known whether granisetron is excreted in human milk. Use of granisetron during pregnancy or lactation should be limited to situations where the

potential benefit to the mother justifies the potential risk to the fetus or nursing infant.

Effects on ability to drive and use machines:
No clinically relevant effects on resting EEG or on the performance of psychometric tests were observed in healthy subjects after i.v. granisetron at any dose tested (up to 200µg/kg). There are no data on the effect of granisetron on the ability to drive or use machinery.

OVERDOSAGE AND TREATMENT:

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

STORAGE:

Store below 30°C. Do not freeze.
Keep in the original outer carton to protect from light.

KEEP OUT OF REACH OF CHILDREN
JAUHI DARI KANAK-KANAK

PACK QUANTITIES:

Available in:
1) 3ml sterile solution in Pre-filled Syringe – 1 syringe & 10 syringes per box
2) 1ml sterile solution in Pre-filled Syringe – 1 syringe & 10 syringes per box

Further information can be obtained from pharmacist, physician or the manufacturer.

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