PRODUCT INFORMATION

Granisetron-AFT

AFT Pharmaceuticals Pty. Ltd.

NAME OF MEDICINE

Granisetron-AFT Solution for Injection 1mg/ml

NAME AND STRENGTH OF ACTIVE SUBSTANCE

Granisetron hydrochloride 3.3501mg/3ml equivalent to 3mg/3ml Granisetron and Granisetron hydrochloride 1.1167mg/ml equivalent to 1mg/ml Granisetron

PRODUCT DESCRIPTION

Granisetron-AFT Solution for Injection 1 mg/ml is a clear, colourless, non-pyrogenic, sterile solution containing Granisetron hydrochloride equivalent to 1mg of Granisetron free base in 1ml and equivalent to 3mg of Granisetron free base in 3ml;

It also contains the sodium chloride 0.9% in water for injections, Citric acid monohydrate and Sodium citrate as the excipients.

A reconstitute solution also shall be clear and colourless.

Granisetron-AFT Solution for Injection is filled in 1ml/5ml colorless Type I glass ampoules. The ampoules are supplied in packs of 1 or 5 ampoules per PVC tray. One tray with 1 or 5 ampoules is packaged into one paper carton.

PHARMACOLOGICAL

Pharmacodynamics properties

Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (5-HT3) antagonists.
ATC code: A04AA02

Mechanism of Action
Serotonin receptors of the 5-HT3 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-HT3 receptors. This invokes vagal afferent discharge, inducing vomiting. Granisetron is a potent antiemetic 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.

Pharmacokinetics properties

Absorption
Absorption of Granisetron is rapid and complete, though oral bioavailability is reduced to about 60% as a result of first pass metabolism. Oral bioavailability is generally not influenced by food.

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 oral and intravenous route is approximately 9 hours, with a wide intersubject variability.

The pharmacokinetics of oral and 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 3 mg 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.

Pharmacokinetics in Special Populations

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

Hepatic impairment:
In patients with hepatic impairment due to neoplastic liver involvement, total plasma clearance of an intravenous dose 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.

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

INDICATION

Granisetron-AFT Solution for Injection 1mg/ml 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

Granisetron is indicated for the prevention of delayed nausea and vomiting associated with chemotherapy and radiotherapy.
Granisetron is indicated in children aged 2 years and above for the prevention and treatment of acute nausea and vomiting associated with chemotherapy.

DOSAGE AND ADMINISTRATION

Standard Dosage Chemotherapy Induced Nausea and Vomiting (CINV)

Adults

Prevention:
A dose of 1 – 3mg (10 – 40 mcg/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 – 40 mcg/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.

Paediatrics

Prevention and treatment:
A dose of 10 – 40 mcg/kg body weight (up to 3mg) should be administered as an intravenous infusion, diluted in 10 to 30ml 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)

Adult

Prevention:
A dose of 1 – 3mg (10 – 40 mcg/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.

Paediatrics

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 anaesthesia.

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

Paediatrics

There is insufficient information to recommend intravenous administration of Granisetron in the prevention and treatment of postoperative nausea and vomiting in paediatric 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.

Preparing the infusion

Adults: The contents of a 1ml ampoule can be diluted to a volume of 5ml; the contents of a 3ml ampoule can be diluted to a volume of 15ml.

Granisetron can also be diluted in 20-50ml compatible infusion fluid and then given over 5 minutes as an intravenous infusion in any of the following solutions:

- 0.9 % w/v sodium chloride injection
- 5 % w/v dextrose injection
- 0.18 % w/v sodium chloride and 4% glucose injection
- 10% mannitol injection

No other diluents should be used.

Children 2 years of age and older: To prepare the dose of 10-40µg/kg, the appropriate volume is withdrawn and diluted with infusion fluid (as for adults) to a total volume of 10-30ml.

As a general precaution, Granisetron should not be mixed in solution with other drugs.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

CONTRAINDICATIONS
Granisetron-AFT Solution for Injection 1 mg/ml is contraindicated in patients with known hypersensitivity to Granisetron or any of 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 with other 5-HT3 antagonists, cases of 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, 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 (see section DRUG INTERACTIONS).

Cross-sensitivity between 5-HT3 antagonists (e.g. Dolasetron, Ondansetron) has been reported. It is recommended that Granisetron are not taken by patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucosegalactose malabsorption.

As with other 5-HT3 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.

Effects on Ability to Drive and Use Machines
Granisetron has no or negligible influence on the ability to drive or to use machines

DRUG INTERACTIONS
Granisetron do 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 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 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-HT3 antagonists, cases of ECG modifications including QT prolongation have been reported with Granisetron. This 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.

As with other 5-HT3 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 (see section WARNINGS AND PRECAUTIONS).

USE IN PREGNANCY AND LACTATION
Pregnancy
There is limited amount of data from the use of Granisetron in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of Granisetron during pregnancy.

Breastfeeding
It is unknown whether Granisetron or its metabolites are excreted in human milk. As a precautionary measure, breastfeeding should not be advised during treatment with Granisetron.

SIDE EFFECTS AND ADVERSE REACTIONS
The most frequently reported adverse reactions for Granisetron are headache and constipation which may be transient. ECG changes including QT prolongation have been reported with Granisetron.

System organ class	Frequency
Immune system disorders	*Uncommon* Hypersensitivity reactions e.g. anaphylaxis, urticaria
Psychiatric disorders	*Common* Insomnia
Nervous system disorders	*Very Common* Headache *Uncommon* Extrapyramidal reactions
Cardiac disorders	*Uncommon* QT interval prolonged
Gastrointestinal disorders	*Very common* Constipation *Common* Diarrhoea
Hepatobiliary disorders	*Common* Transaminases increased*
Skin and subcutaneous tissue disorders	*Uncommon* Rash

Description of selected adverse reactions
As for other 5-HT3 antagonists, ECG changes including QT prolongation have been reported with Granisetron (see sections WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

OVERDOSE AND TREATMENT
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 38.5mg of Granisetron as a single injection have been reported, with symptoms of mild headache but no other reported sequelae.

INCOMPATIBILITIES
As a general precaution, Granisetron-AFT Solution for Injection 1 mg/ml should not be mixed with other medicinal products except those compatible solutions mentioned in **Method of Administration**

STORAGE AND SHELF LIFE
Shelf life
3 years (36 months) from the date of manufacture.

Storage
Store below 30ºC. Do not refrigerate or freeze.
Store in the outer carton in order to protect from light.

Keep the ampoules in outer carton and only taken out prior to use.
Ampoules removed from the pack should be protected from light.

The product should be used immediately after opening.
For single use only. Discard any remaining portion.

Shelf life after dilution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C in normal indoor illumination protected from direct sunlight. 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 - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

PRESENTATION
Granisetron-AFT Solution for Injection is available in the following pack size:
1mg/ml: Packed in box of 1 ampoule and 5 ampoules.
3mg/3ml: Packed in box of 1 ampoule and 5 ampoules.

Primary Container Type:
1 ml or 5 ml, Colorless, Type I glass ampoule

Secondary Container Type:
The ampoules are supplied in packs of 1 or 5 ampoules per PVC tray.
One tray with 1 or 5 ampoules is packaged into one printed paper carton.

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