PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

GRANISETRON 1 mg/mL (1 mL) FRESENIUS

GRANISETRON 1 mg/mL (3 mL) FRESENIUS

Concentrate for solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

GRANISETRON 1 mg/mL (1 mL) FRESENIUS contains granisetron hydrochloride equivalent to 1 mg granisetron.

GRANISETRON 1 mg/mL (3 mL) FRESENIUS contains granisetron hydrochloride equivalent to 3 mg granisetron.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for injection/infusion.

A clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GRANISETRON FRESENIUS is indicated for the prevention and treatment of nausea and vomiting induced by cytostatic therapy (chemotherapy and radiotherapy) and for the prevention and treatment of post-operative nausea and vomiting.

4.2 Posology and method of administration

Posology

Chemotherapy induced nausea and vomiting (CINV)

Adults:

Intravenous:

Prevention: A dose of 1 – 3 mg (10 – 40 µg/kg) of GRANISETRON FRESENIUS 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 – 40 µg/kg) of GRANISETRON FRESENIUS 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 FRESENIUS may be administered, if required, at least 10 minutes apart. The maximum dose of GRANISETRON FRESENIUS to be administered over 24 hours should not exceed 9 mg.

Intramuscular:

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

Paediatrics (children of 2 years and older):

Intravenous:

A dose of 10 – 40 µg/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 FRESENIUS by the intramuscular route in children.

Radiotherapy induced nausea and vomiting (RINV)

Adults:

Intravenous:

Prevention: A dose of 1 – 3 mg (10 – 40 µg/kg) of GRANISETRON FRESENIUS 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 the use of GRANISETRON FRESENIUS in the prevention and treatment of RINV in children.

Post operative nausea and vomiting (PONV)

Adults:

Intravenous:

Prevention:

A dose of 1 mg (10 µg/kg) of GRANISETRON FRESENIUS should be administered as a slow intravenous injection (over 30 seconds) prior to induction of anaesthesia.

Treatment:

A dose of 1 mg (10 µg/kg) of GRANISETRON FRESENIUS should be administered by slow intravenous injection (over 30 seconds). The maximum dose for patients undergoing anaesthesia for surgery is a total dose of 3 mg GRANISETRON FRESENIUS intravenous in one day.

Paediatrics:

There is insufficient information to recommend the use of GRANISETRON FRESENIUS in the prevention and treatment of PONV in children.

Elderly:

No dosage adjustment required.

Renal impairment:

No dosage adjustment required.

Hepatic impairment:

No dosage adjustment required.

Method of administration

Intravenous infusion, slow intravenous injection or intramuscular injection.
Prophylactic administration of GRANISETRON FRESENIUS should be completed prior to the start of cytostatic therapy or induction of anaesthesia.

For instructions on preparing the injection and for compatibility of GRANISETRON FRESENIUS with infusion fluids, see section 6.6.

4.3 Contraindications

- Hypersensitivity to granisetron or to any of the excipients of GRANISETRON FRESENIUS (see section 6.1).
- Children under the age of 2 years.
- Congenital long QT syndrome.

4.4 Special warnings and precautions for use

GRANISETRON FRESENIUS may reduce intestinal motility. Patients showing symptoms of sub-acute intestinal obstruction or ileus following administration of GRANISETRON FRESENIUS should be monitored carefully.

5-HT_3 antagonists, such as GRANISETRON FRESENIUS, may be associated with dysrhythmias or ECG abnormalities including QT interval prolongation. This potentially may have clinical significance in patients with pre-existing dysrhythmias or cardiac conduction disorders or patients who are being treated with anti-dysrhythmic medicines or beta-blockers. Caution should be exercised in patients with cardiac co-morbidities, patients on cardiotoxic chemotherapy and/or with concomitant electrolyte abnormalities (see section 4.5).

Cases of myocardial ischaemia have been reported in patients treated with serotonin receptor antagonists. In some patients, especially in the case of intravenous administration, symptoms appeared immediately after administration of a serotonin receptor antagonist (e.g. granisetron). Patients should be alerted to the signs and symptoms of myocardial ischaemia.

Cross-sensitivity between 5-HT_3 antagonists (e.g. dolasetron, ondansetron) has been reported.

There have been reports of serotonin syndrome with the use of 5-HT_3 antagonists either alone, but mostly in combination with other serotonergic medicines (including selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs)). Appropriate observation of patients for serotonin syndrome-like symptoms is advised.

No special precautions are required for the elderly or renally and/or hepatically impaired patients. Owing to kinetics a degree of caution should be exercised in using GRANISETRON FRESENIUS with this category.

Sodium content

GRANISETRON FRESENIUS contains 3,57 mg sodium per mL, equivalent to 0,2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

As for other 5-HT_3 antagonists, cases of ECG modifications including QT prolongation have been reported with GRANISETRON FRESENIUS. In patients concurrently treated with medicines known to prolong the QT interval and/or which are dysrhythmogenic, this may lead to clinical consequences (see section 4.4). This may also have clinical significance in patients who are being treated with anti-dysrhythmic medicines or beta-blockers (see section 4.4).

In vitro, it could be shown that metabolism of GRANISETRON FRESENIUS is inhibited by ketoconazole, a potent CYP3A inhibitor. Co-administration of GRANISETRON FRESENIUS with systemic ketoconazole may, therefore, increase the elimination half-life of GRANISETRON FRESENIUS.

In humans, hepatic enzyme induction with phenobarbital resulted in an increase in total plasma clearance of GRANISETRON FRESENIUS of approximately 25 %. The clinical significance of this change is not known.

No interaction was found between GRANISETRON FRESENIUS and benzodiazepines (lorazepam), neuroleptics (haloperidol) or anti-ulcer medicines (cimetidine). Additionally, GRANISETRON FRESENIUS has not shown any apparent medicine interaction with emetogenic cancer chemotherapies.

No specific interaction studies have been conducted in anaesthetised patients.

There have been reports of serotonin syndrome following concomitant use of 5-HT_3 antagonists and other serotonergic medicines (including SSRIs and SNRIs) (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited data on the use of GRANISETRON FRESENIUS 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 FRESENIUS during pregnancy.

Breastfeeding

There is no data on the excretion of GRANISETRON FRESENIUS in breast milk. As a precautionary measure, breastfeeding is not advisable during treatment with GRANISETRON FRESENIUS.

Fertility

In rats, GRANISETRON FRESENIUS had no harmful effects on reproductive performance or fertility.

4.7 Effects on ability to drive and use machines

Special care should be taken with patients performing tasks requiring concentration as somnolence may occur.

4.8 Undesirable effects

a) Summary of the safety profile

The most frequently reported adverse reactions for GRANISETRON FRESENIUS are headache and constipation which may be transient. ECG changes including QT prolongation have been reported with GRANISETRON FRESENIUS (see sections 4.4 and 4.5).

System organ class	**Frequent**	**Less frequent**
Immune system disorders		Hypersensitivity reactions Anaphylaxis* Shortness of breath* Hypotension* Urticaria* Oedema Facial oedema
Nervous system disorders	Headache Somnolence Agitation Anxiety Insomnia Taste disorder	Extrapyramidal reactions Dystonia Dyskinesia Serotonin syndrome
Eye disorders		Abnormal vision

Ear and labyrinth disorders	Dizziness	
Cardiac disorders		Dysrhythmias Sinus bradycardia Atrial fibrillation AV-block Ventricular ectopy Non-sustained tachycardia ECG abnormalities QT interval prolonged Myocardial ischaemia (see section 4.4)
Vascular disorders	Hypertension	Hypotension
Gastrointestinal disorders	Constipation Diarrhoea Anorexia	
Hepatobiliary disorders	Raised transaminase levels[1]	Abnormal hepatic function
Skin and subcutaneous tissue disorders		Skin rash Local irritation at administration site**
General disorders and administrative site conditions	Fever Asthenia	

b) Tabulated list of adverse reactions

* Hypersensitivity reactions.

** After repeated intravenous administration.

c) Description of selected adverse reactions

As for other 5-HT_3 antagonists, ECG changes including QT prolongation have been reported with GRANISETRON FRESENIUS (see sections 4.4 and 4.5).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Healthcare providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9 Overdose

Overdosage of up to 38,5 mg of GRANISETRON FRESENIUS (more than 10 times the recommended dose) as a single injection has been reported without symptoms or only the occurrence of a slight headache. There is no specific antidote for GRANISETRON FRESENIUS overdosage. In case of overdosage, symptomatic treatment should be given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 5.7.2 Anti-emetics and anti-vertigo preparations.

Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (5-HT_3) antagonists.
ATC code: A04AA02.

Mechanism of action:

Granisetron is an anti-emetic and selective antagonist of 5-hydroxytryptamine (5-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.

5.2 Pharmacokinetic properties

Absorption:

Following intravenous doses in the range of 20 - 160 µg/kg, plasma pharmacokinetics (C_{max} and AUC) were generally dose-proportional in both healthy subjects and in patients receiving chemotherapy. The mean plasma half-life is 5,2 hours in healthy patients and 8,7 hours in patients receiving chemotherapy, with a wide inter-subject variability.

Distribution:

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

Biotransformation:

Biotransformation pathways include 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 faeces as metabolites.

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

In children, after a single IV dose, the pharmacokinetics resembles that of adults when relevant parameters (volume of distribution, plasma clearance) are adjusted for body weight.

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 plasma clearance of an intravenous dose was approximately halved compared to patients without hepatic involvement. Despite these changes, no dosage adjustment is necessary.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Citric acid monohydrate

Sodium hydroxide (for pH-adjustment)

Hydrochloric acid (for pH-adjustment)

Water for injection.

6.2 Incompatibilities

GRANISETRON FRESENIUS should not be mixed in solution with other medicines, except those mentioned in section 6.6.

No interactions with GRANISETRON FRESENIUS have been recorded with multiple chemotherapy regimes, including cisplatin up to 120 mg/m^2.

6.3 Shelf life

Unopened: 3 years

After opening: The product must be used immediately after first opening.

After dilution: The product should be used immediately. Chemical and physical in-use stability has been demonstrated for 24 hours at 25 °C protected from direct sunlight.

From a microbiological point of view, the solutions 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 under controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at or below 25 °C. Do not freeze.

Keep the ampoules in the outer carton to protect from light.

For storage after opening or dilution, see section 6.3.

6.5 Nature and contents of container

1 mL or 3 mL clear Type I glass ampoules packed into an outer carton in the following pack sizes:

5 x 1 mL; 10 x 1 mL

5 x 3 mL; 10 x 3 mL

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

GRANISETRON FRESENIUS is compatible with the following infusion fluids:

0,9 % *m/v* sodium chloride;

0,18 % *m/v* sodium chloride and 4 % *m/v* dextrose;

5 % *m/v* dextrose;

Hartmann’s solution;

sodium lactate;

10 % *m/v* mannitol.

Preparing the injection:

Adults:

To prepare the dose of GRANISETRON FRESENIUS (3 mL), the contents of one ampoule (3 mg) or 40 µg/kg is withdrawn from the ampoule and diluted with infusion fluid (as listed above), to a total volume of 20 - 50 mL.

Children:

To prepare the dose of 10 - 40 µg/kg the appropriate volume (up to 3 mL) from the 3 mg ampoule or up to 1 mL from the single use ampoule is withdrawn and diluted with infusion fluid (as listed above) to a total volume of 10 to 30 mL.

GRANISETRON FRESENIUS is for single use only. Discard any unused portion.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Limited

Stand 7, Growthpoint Business Park

162 Tonetti Street

Halfway House Extension 7

Midrand 1685

Gauteng

South Africa

Telephone number: +27 (0)11 545 0000

8. REGISTRATION NUMBER

GRANISETRON 1 mg/mL (1 mL) FRESENIUS: 44/5.7.2/0671

GRANISETRON 1 mg/mL (3 mL) FRESENIUS: 44/5.7.2/0672

9. DATE OF FIRST AUTHORISATION

02 October 2014

10. DATE OF REVISION OF THE TEXT

29 March 2023