

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Granisetron 1 mg/ml concentrate for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml concentrate for solution for injection or infusion contains 1.12 mg granisetron hydrochloride equivalent to 1 mg granisetron.

3 ml concentrate for solution for injection or infusion contains 3.36 mg granisetron hydrochloride equivalent to 3 mg granisetron.

Excipients:

Up to 4.5 mg of sodium per 1 ml solution

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for injection or infusion

The product is a clear and colourless solution. The pH value of the solution is adjusted to 5 (nominal range: 4 – 6), its osmolality is 318 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Granisetron is indicated for the prevention or treatment of nausea and vomiting induced by chemotherapy or radiotherapy in adults and children, 2 years of age and older.

4.2 Posology and method of administration

Granisetron is for intravenous administration only.

Adults The dose can be administered as an intravenous bolus over not less than 30 seconds diluted with a compatible infusion fluid. The contents of a 1 ml ampoule can be diluted to a volume of 5 ml; the contents of a 3 ml ampoule can be diluted to a volume of 15 ml.

Granisetron can also be diluted in 20 to 50 ml of infusion fluid and then administered over 5 minutes.

For further instructions regarding preparation see section 6.6.

Prevention

The recommended dose of Granisetron is 1 mg or 3 mg depending on the emetogenic potential of the chemotherapy or radiotherapy. In clinical trials, the majority of patients required only a single dose of Granisetron to control nausea and vomiting over 24 hours.

There is clinical experience in patients receiving daily administration for up to five consecutive days in one course of therapy.

It is recommended to administer the dose not more than 30 minutes before the start of cytostatic therapy. Prophylactic administration of Granisetron should be completed prior to the start of cytostatic therapy.

Treatment

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

Maximum daily dose

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 corticosteroids

The efficacy of granisetron may be enhanced by the addition of dexamethasone (8 – 20 mg) or methylprednisolone (250 mg).

Children 2 years of age and older

Prevention

A single dose of Granisetron of 20 – 40 µg/kg body weight (up to 3 mg) should be administered by intravenous infusion, diluted in 10 mL to 30 mL of compatible infusion fluid and administered over 5 minutes.

For further instructions regarding preparation see section 6.6.

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 for prevention.

An additional dose of 40 µg/kg (up to 3 mg) may be administered within a 24 hour period either as a single dose or as two divided doses. This additional dose should be administered at least 10 minutes apart from the initial infusion.

There are no sufficient data in children under 2 years of age. Therefore Granisetron should not be used in children below 2 years of age.

Elderly

No special requirements apply to elderly patients.

Patients with renal or hepatic impairment

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

4.3 Contraindications

Hypersensitivity to granisetron, to related substances (e.g. ondansetron) or to any of the excipients of Granisetron (see section 6.1).

4.4 Special warnings and precautions for use

Granisetron may reduce intestinal motility. Patients showing symptoms of sub-acute intestinal obstruction following administration of Granisetron should be monitored carefully.

No special precautions are required for elderly patients or renally and/or hepatically impaired patients. Although to date no signs of an increased incidence of adverse events have been observed in hepatically impaired patients, owing to the kinetics a degree of caution should be exercised in using granisetron with this category.

5-HT₃ antagonists such as granisetron may be associated with arrhythmias or ECG abnormalities. This potentially may have clinical significance in patients with pre-existing arrhythmias or cardiac conduction disorders or patients who are being treated with antiarrhythmic agents or beta-blockers.

This medicinal product contains up to 4.5 mg sodium per 1 ml solution. This should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No definitive drug-drug interaction study has been performed. Granisetron is primarily metabolised by CYP3A enzymes and does not induce or inhibit any other CYP enzymes. In vitro, it could be shown that metabolism of granisetron is inhibited by ketoconazole, a potent CYP3A inhibitor. Coadministration of granisetron with systemic ketoconazole may, therefore, increase granisetron's elimination half-life. In humans, hepatic enzyme induction with phenobarbital resulted in an increase in total plasma clearance of granisetron of approximately 25 %. The clinical significance of this change is not known.

Granisetron injections have been safely administered in patients treated with benzodiazepines, neuroleptics and anti-ulcer medications and is commonly prescribed with antiemetic treatments. Granisetron injections have 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.

4.6 Pregnancy and lactation

Pregnancy

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.

Lactation

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

4.7 Effects on ability to drive and use machines

Somnolence is a common side effect observed after granisetron treatment. Depending on the patient's individual reaction this may impair his/her ability to drive, to operate machinery or to work at high altitude. If the patient feels drowsy after treatment with Granisetron he/she should be advised not to drive, not to operate machinery and not to carry out any work that requires a safe foothold.

4.8 Undesirable effects

The most frequent adverse effect is headache, occurring in about 14% of patients. Other less common adverse events associated with granisetron administration include hypersensitivity reactions (e.g. anaphylaxis), constipation, diarrhoea, asthenia and somnolence.

The frequency of side effects is classified into the following categories:

Very common	$\geq 1/10$
Common	$\geq 1/100, < 1/10$
Uncommon	$\geq 1/1000, < 1/100$
Rare	$\geq 1/10\ 000, < 1/1000$
Very rare	$< 1/10\ 000$, not known (cannot be estimated from the available data)

Incidence and severity are given in the following table:

Cardiac disorders	<u>Rare</u> : arrhythmias such as sinus bradycardia, atrial fibrillation, varying degrees of AV-block, ventricular ectopy (including non-sustained tachycardia), ECG abnormalities
Nervous system disorders	<u>Very common</u> : headache <u>Common</u> : somnolence, agitation, anxiety, insomnia, taste disorder <u>Rare</u> : dystonia and dyskinesia have been reported with medicines in the 5-HT ₃ antagonist class
Eye disorders	<u>Uncommon</u> : abnormal vision
Ear and labyrinth disorders	<u>Common</u> : dizziness
Gastrointestinal disorders	<u>Common</u> : diarrhoea, constipation, anorexia
Skin and subcutaneous tissue disorders	<u>Uncommon</u> : skin rashes <u>Rare</u> : local irritation at administration site after repeated intravenous administration
Vascular disorders	<u>Common</u> : hypertension <u>Rare</u> : hypotension
General disorders	<u>Common</u> : fever, asthenia
Immune system disorders	<u>Rare</u> : hypersensitivity reactions, sometimes severe (e.g., anaphylaxis, shortness of breath, hypotension, urticaria) <u>Very rare</u> : oedema (including facial oedema)
Hepatobiliary disorders	<u>Rare</u> : <u>abnormal hepatic function, raised transaminase levels</u>

4.9 Overdose

Overdosage of up to 30 mg of granisetron injection (10 times the recommended dose) has been reported without symptoms or only the occurrence of a slight headache. There is no specific antidote for granisetron overdosage. In case of overdosage, symptomatic treatment should be given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group (ATC code): Serotonin (5-HT₃) antagonists (A04AA02)

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-ray irradiation.

5.2 Pharmacokinetic properties

General Characteristics

Absorption

Following intravenous doses in the range of 20-160 mcg/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 was 5.2 h in healthy subjects and 8.7 h in patients receiving chemotherapy.

Distribution

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

Biotransformation

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 the dose whilst that of the metabolites amounts to about 47% of the dose. The remainder is excreted in the faeces as metabolites. Mean plasma half-life in patients is approximately nine hours, with a wide inter-subject variability.

Characteristics in patients

The plasma concentration of Granisetron is not clearly correlated with its antiemetic 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 plasma clearance of an intravenous dose was approximately halved compared to patients without hepatic involvement. Despite these changes, no dosage adjustment is necessary.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, carcinogenicity, reproductive toxicity and genotoxicity.

A study in cloned human cardiac ion channels has shown that granisetron has the potential to affect cardiac repolarisation via blockade of HERG potassium channels. Granisetron has been shown to block both sodium and potassium channels, which potentially affects both depolarization and repolarization through prolongation of PR, QRS, and QT intervals. If changes do occur, they are generally without clinical significance. This data helps to clarify the molecular mechanisms by which some of the ECG changes (particularly QT and QRS prolongation) associated with this class of agents occur. However, there is no modification of the cardiac frequency, blood pressure or ECG trace.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Citric acid monohydrate
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

30 months

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

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 to be stored, the dilutions should be prepared under appropriate aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C.
Do not freeze.
Keep the ampoules in the outer carton in order to protect from light.
For storage conditions of the diluted medicinal product see section 6.3.

6.5 Nature and contents of container

1 and 3 ml colourless ampoules.

Pack sizes: 5 x 1 ml, 10 x 1 ml, 5 x 3 ml and 10 x 3 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Preparing the infusion

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

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

0.9 % w/v sodium chloride injection

0.18 % w/v sodium chloride and 4% glucose injection

5 % w/v glucose injection

Hartmann's solution

1.87 % w/v sodium lactate injection

10% mannitol injection

1.4% w/v sodium hydrogen carbonate injection

2.74% w/v sodium hydrogen carbonate injection

4.2% w/v sodium hydrogen carbonate injection

No other diluents should be used.

Children 2 years of age and older: To prepare the dose of 20 - 40 µg/kg, the appropriate volume is withdrawn and diluted with infusion fluid (as for adults) to a total volume of 10 to 30 ml.

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

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

7 MARKETING AUTHORISATION HOLDER

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Langes Feld 13

31789 Hameln

Germany

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PL 25215/0019

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