Granodex
Solution for injection

Composition:
Each ml of solution for injection contains
Granisetron HCl equivalent to Granisetron 1 mg

List of Excipients:
Sodium chloride, citric acid monohydrate, sodium hydroxide, water for injection.

Product Description:
Clear, colorless solution.

Pharmacodynamics:
ATC code: A04AA02
Granisetron is a potent and highly selective 5-hydroxytryptamine ($5\text{-}HT_3$) receptor antagonist with antiemetic activity.

Pharmacokinetics:
Absorption
Absorption of granisetron is generally not influenced by food and is rapid and complete, though oral bioavailability is reduced to around 60% as a result of first-pass metabolism.

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

Metabolism
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 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 is approximately 9 hours, with a wide intersubject variability.

Indications:
Granisetron is indicated for the prevention or treatment of nausea and vomiting induced by cytostatic therapy and for the prevention and treatment of postoperative nausea and vomiting.

Recommended Dosage:
Cytostatic therapy
Adults
3 mg granisetron which should be administered either in 15 ml infusion fluid as an intravenous bolus over not less than 30 seconds or diluted in 20 to 50 ml infusion fluid and administered over five minutes.

Prevention:
The majority of patients have required only a single dose of granisetron to control nausea and vomiting over 24 hours. Up to two additional doses of 3 mg granisetron may be administered within a 24-hour period. There is clinical experience in patients receiving daily administration for up to five consecutive days in one course of therapy. Prophylactic administration of granisetron should be completed prior to the start of cytostatic therapy.

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

Maximum daily dosage:
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 dexamethasone
The efficacy of granisetron may be enhanced by the addition of dexamethasone.

Elderly
No special requirements apply to elderly patients.

Children
Prevention:
A single dose of 40 mcg/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 five minutes. 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 prevention.
One additional dose of 40 mcg/kg body weight (up to 3 mg) may be administered within a 24-hour period. This additional dose should be administered at least 10 minutes apart from the initial infusion.

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

Preparation of infusion
Granisetron solution for injection or infusions must be prepared at the time of administration and under appropriate aseptic conditions.

Adults:
To prepare a dose of 3 mg, 3 ml is withdrawn from the ampoule and diluted either to 15 ml with 0.9% sodium chloride (for bolus administration) or in a compatible infusion fluid to a total volume of 20 to 50 ml, in any of the following solutions: 0.9% sodium chloride, Ringer's lactate, 5% dextrose and 20% mannitol solution. The mixtures solutions are stable within 24 hours at temperatures below 30ºC.

Children:
The appropriate dose is diluted with a compatible infusion fluid (as for adults) to a total volume of 10 to 30 ml, in any of the following solutions: 0.9% sodium chloride, Ringer's lactate, 5% dextrose and 20% mannitol solution. The mixtures solutions are stable within 24 hours at temperatures below 30ºC.

Postoperative nausea and vomiting
Adults
Prevention:
For prevention in adults, a single dose of 1 mg of granisetron should be diluted to 5 ml and administered as a slow intravenous injection (over 30 seconds). Administration should be completed prior to induction of anesthesia.

Treatment:
For the treatment of established postoperative nausea and vomiting in adults, a single dose of 1 mg of granisetron should be diluted to 5 ml and administered by slow intravenous injection (over 30 seconds).

Maximum dose and duration of treatment:
Two doses (2 mg) in one day.

Preparation of injection
Adults:
To prepare a dose of 1 mg, 1 ml should be withdrawn from the ampoule and diluted to 5 ml with 0.9% sodium chloride. No other diluents should be used.

Children:
There is no experience in the use of granisetron in the prevention and treatment of postoperative nausea and vomiting in children. Granisetron is not therefore recommended for the treatment of postoperative nausea and vomiting in this age group.

Elderly patients
As for adults.

Renally impaired and hepatically impaired patients
As for adults.

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Route of Administration: intravenous injection or infusion.

Contraindication:
Granisetron is contraindicated in patients with known hypersensitivity to granisetron or to any of its excipients.

Warnings and Precautions:
- As granisetron may reduce lower bowel motility, patients with signs of subacute intestinal obstruction should be monitored closely following administration of granisetron.
- As with other 5-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 with preexisting arrhythmias or cardiac conduction disorders, this might lead to clinical consequences. Therefore, caution should be exercised in patients with cardiac comorbidities, on cardiotoxic chemotherapy and/or with concomitant electrolyte abnormalities. Cross-sensitivity between 5-HT_3 antagonists has been reported.
- As with other 5-HT_3 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.
- There has been no evidence from human studies that granisetron has any adverse effect on alertness.
- As a general precaution, granisetron should not be mixed in solution with other drugs. Prophylactic administration of granisetron should be completed prior to the start of cytostatic therapy or induction of anesthesia.
- Data from two-year carcinogenicity studies have shown an increase in hepatocellular carcinoma and/or adenoma in rats and mice of both sexes given 50 mg/kg (rat dosage reduced to 25 mg/kg/day at week 59).
  Increases in hepatocellular neoplasia were also detected at 5 mg/kg in male rats. In both species, drug-induced effects (hepatocellular neoplasia) were not observed in the low-dose group (1 mg/kg). In several *in vitro* and *in vivo* assays, granisetron was shown to be nongenotoxic in mammalian cells.

Interactions with Other Medicines and Other Forms of Interaction:
- No evidence of any interaction has been indicated between granisetron and cimetidine or lorazepam.
- Granisetron has been safely administered with commonly used anesthetic and analgesic agents. In addition, *in vitro* human microsomal studies have shown that 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-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 are arrhythmogenic, this may lead to clinical consequences.
- As with other 5-HT_3 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.

Use during Pregnancy and Lactation:
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. There are no data on the excretion of granisetron in breast milk. Breastfeeding should therefore be discontinued during therapy.

Adverse Effects:
Summary of the safety profile
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. The following table of listed adverse reactions is derived from clinical trials and postmarketing data associated with granisetron.

Frequency categories are as follows:
Very common: ≥1/10
Common: ≥1/100 to <1/10
Uncommon: ≥1/1,000 to <1/100
Rare: ≥1/10,000 to <1/1,000
Very rare: <1/10,000

Immune system disorders	
Uncommon	Hypersensitivity reactions e.g. anaphylaxis, urticaria
Nervous system disorders	
Very common	Headache
Uncommon	Serotonin syndrome
Cardiac disorders	
Uncommon	QT prolongation
Gastrointestinal disorders	
Very common	Constipation
Hepatobiliary disorders	
Common	Elevated hepatic transaminases
Skin and subcutaneous tissue disorders	
Uncommon	Rash

Granisetron has been generally well-tolerated. As reported with other drugs of this class, headache and constipation have been the most frequently noted adverse events, but the majorities have been mild or moderate in nature. Cases of hypersensitivity reaction, occasionally severe (e.g. anaphylaxis) have been reported. Other allergic reactions including minor skin rashes have also been reported. Transient increases in hepatic transaminases, generally within the normal range, have been seen.

As for other 5-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.

As with other 5-HT_3 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.

Overdose and Treatment:
There is no specific antidote for granisetron. In the case of overdosage, symptomatic treatment should be given. One patient has received 30 mg of granisetron intravenously. The patient reported a slight headache but no other sequelae were observed.

Incompatibilities:
This medicinal product must not be mixed with other medicinal products except 0.9% sodium chloride, Ringer's lactate, 5% dextrose and 20% mannitol solution.

ON MEDICAL PRESCRIPTION ONLY.

STORE AT TEMPERATURES BELOW 30ºC.

Shelf Life After Reconstitution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 30ºC. 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 to 8ºC, unless dilution has taken place in controlled and validated aseptic conditions.

Presentation and registration number:
Box, 5 glass type I clear ampoules x 3 ml; SIN16589P

Manufactured by
PT Ferron Par Pharmaceuticals
Cikarang-Indonesia

For
PT Dexa Medica
Jl. Jend. Bambang Utoyo No. 138
Palembang-Indonesia

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