Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Granisetron Martindale Pharma 1mg/1ml Concentrate for Solution for Injection/Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is granisetron

Each ml solution for injection contains 1 mg of granisetron (as the hydrochloride).

Each 1ml of concentrate contains 9 mg of sodium chloride, equivalent to 3.54 mg of sodium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for injection/infusion.

The solution for injection/infusion is a sterile, clear and colourless liquid, with a pH of 4.0 – 6.0. The osmolarity of the product is approximately 310 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Granisetron Martindale Pharma is indicated in adults for the prevention and treatment of

- acute nausea and vomiting associated with chemotherapy and radiotherapy.
- post-operative nausea and vomiting.

Granisetron Martindale Pharma solution for injection is indicated for the prevention of delayed nausea and vomiting associated with chemotherapy and radiotherapy.

Granisetron Martindale Pharma solution for injection is indicated in children aged 2 years and above for the prevention and treatment of acute nausea and vomiting associated with chemotherapy.

4.2 Posology and method of administration

Posology
Chemo- and radiotherapy-induced nausea and vomiting (CINV and RINV)

Prevention (acute and delayed nausea)
A dose of 1-3 mg (10-40 μg/kg) of Granisetron Martindale Pharma solution for injection should be administered either as a slow intravenous injection or as a diluted intravenous infusion 5 minutes prior to the start of chemotherapy. The solution should be diluted to 5ml per mg.

Treatment (acute nausea)
A dose of 1-3 mg (10-40 μg/kg) of Granisetron Martindale Pharma solution for injection should be administered. Further maintenance doses of Granisetron Martindale Pharma solution for injection may be administered at least 10

minutes apart. The maximum dose to be administered over 24 hours should not exceed 9mg.

Combination with adrenocortical steroid
The efficacy of parenteral granisetron may be enhanced by an additional intravenous dose of an adrenocortical steroid e.g. by 8-20 mg dexamethasone administered before the start of the cytostatic therapy or by 250 mg methyl-prednisolone administered prior to the start and shortly after the end of the chemotherapy.

Paediatric population
The safety and efficacy of Granisetron Martindale Pharma solution for injection in children aged 2 years and above has been well established for the prevention and treatment (control) of acute nausea and vomiting associated with chemotherapy and the prevention of delayed nausea and vomiting associated with chemotherapy. A dose of 10-40 µg/kg body weight (up to 3 mg) should be administered as an i.v. infusion, diluted in 10-30 ml infusion fluid and administered over 5 minutes prior to the start of chemotherapy. One additional dose may be administered within 24 hour-period if required. This additional dose should not be administered until at least 10 minutes after the initial infusion.

Post-operative nausea and vomiting (PONV)
A dose of 1 mg (10 µg/kg) of Granisetron Martindale Pharma solution for injection should be administered by slow intravenous injection. The maximum dose of Granisetron Martindale Pharma to be administered over 24 hours should not exceed 3 mg. For the prevention of PONV, administration should be completed prior to induction of anaesthesia.

Special populations

Elderly and renal impairment
There are no special precautions required for its use in either elderly patients or those patients with renal or hepatic impairment.

Hepatic Impairment
There is no evidence to date for an increased incidence of adverse events in patients with hepatic disorders. On the basis of its kinetics, whilst no dosage adjustment is necessary, granisetron should be used with a certain amount of caution in this patient group.

Method of administration
Administration may be as either 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.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients.

4.4 Special warnings and precautions for use

Granisetron Martindale Pharma may reduce lower bowel motility; patients with signs of sub-acute intestinal obstruction should be monitored following its administration.

As for other 5-HT_3 antagonists, ECG changes including QT interval prolongation have been reported with granisetron. 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 cardiotoxic chemotherapy and/or with concomitant electrolyte abnormalities (see section 4.5).
Cross-sensitivity between 5-HT_3 antagonists (e.g. dolasetron, ondansetron) has been reported.

This medicinal product contains less than 1 mmol sodium (23 mg) per 1 ml, i.e. essentially ‘sodium free’.

4.5 Interaction with other medicinal products and other forms of interaction

As for other 5-HT_3 antagonists, cases of ECG modifications including QT prolongation have been reported with granisetron. In patients concurrently treated with medicinal products known to prolong QT interval and/or which are arrhythmogenic, this may lead to clinical consequences (see section 4.4).

In studies in healthy subjects, no evidence of any interactions has been indicated between granisetron and benzodiazepines (lorazepam), neuroleptics (haloperidol) or anti-ulcer medicinal products (cimetidine). Additionally, granisetron has not shown any apparent medicinal product interaction with emetogenic cancer chemotherapies.

No specific interaction studies have been conducted in anaesthetised patients.

4.6 Fertility, 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 (see section 5.3). As a precautionary measure**,** it is preferable to avoid the use of granisetron during pregnancy.

Breast-feeding
It is unknown whether granisetron or its metabolites are excreted in human milk. As a precautionary measure, breast-feeding should not be advised during treatment with Granisetron Martindale Pharma.

Fertility
In rats, granisetron had no harmful effects on reproductive performance or fertility.

4.7 Effects on ability to drive and use machines

Granisetron Martindale Pharma is not expected to impair the ability to drive or to use machines.

4.8 Undesirable effects

Summary of the safety profile
The most frequently reported adverse reactions for Granisetron Martindale Pharma are headache and constipation which may be transient. ECG changes including QT prolongation have been reported with Granisetron Martindale Pharma (see sections 4.4 and 4.5).

Tabulated summary of adverse reactions
The following table of listed adverse reactions is derived from clinical trials and post-marketing data associated with Granisetron Martindale Pharma and other 5-HT_3 antagonists.

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
Psychiatric disorders	
Common	Insomnia
Nervous system disorders	

Very common	Headache
Uncommon	Extrapyramidal Reactions
Cardiac disorders	
Uncommon	QT prolongation
Gastrointestinal disorders	
Very common	Constipation
Common	Diarrhoea
Hepatobiliary disorders	
Common	Elevated hepatic transaminases*
Skin and subcutaneous tissue disorders	
Uncommon	Rash

*Occurred at a similar frequency in patients receiving comparator therapy

Description of selected adverse reactions
As for other 5-HT_3 antagonists, ECG changes including QT prolongation have been reported with granisetron (see sections 4.4 and 4.5).

4.9 Overdose

There is no specific antidote for Granisetron Martindale Pharma. In the case of overdose with the injection, symptomatic treatment should be given. Doses of up to 38.5 mg of Granisetron Martindale Pharma as a single injection have been reported, with symptoms of mild headache, but no other reported sequelae.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Neurological mechanisms, serotonin-mediated nausea and vomiting
Serotonin is the main neurotransmitter responsible for emesis after chemo- or radio-therapy. The 5-HT_3 receptors are located in three sites: vagal nerve terminals in the gastrointestinal tract and chemoreceptor trigger zones located in the *area postrema* and the *nucleus tractus solidarius* of the vomiting centre in the brainstem. The chemoreceptor trigger zones are located at the caudal end of the fourth ventricle (*area postrema*). This structure lacks an effective blood-brain barrier, and will detect emetic agents in both the systemic circulation and the cerebrospinal fluid. The vomiting centre is located in the brainstem medullary structures. It receives major inputs from the chemoreceptor trigger zones, and a vagal and sympathetic input from the gut.

Following exposure to radiation or catotoxic substances, serotonin (5-HT) is released from enterochromaffine cells in the small intestinal mucosa, which are adjacent to the vagal afferent neurons on which 5-HT_3 receptors are located. The released serotonin activates vagal neurons via the 5-HT_3 receptors which lead ultimately to a severe emetic response mediated via the chemoreceptor trigger zone within the *area postrema*.

Mechanism of action
Granisetron is a potent anti-emetic and highly 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.

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 to 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.

Pharmacological properties of granisetron
Interaction with neurotropic and other active substances through its activity on P 450-cytochrome has been reported (see section 4.5).

In vitro studies have shown that the cytochrome P450 sub-family 3A4 (involved in the metabolism of some of the main narcotic agents) is not modified by granisetron. Although ketaconazole was shown to inhibit the ring oxidation of granisetron *in vitro*, this action is not considered clinically relevant.

Although QT-prolongation has been observed with 5-HT_3 receptors antagonists (see section 4.4), this effect is of such occurrence and magnitude that it does not bear clinical significance in normal subjects. Nonetheless it is advisable to monitor both ECG and clinical abnormalities when treating patients concurrently with drugs known to prolong the QT (see section 4.5).

Paediatric use
Clinical application of granisetron was reported by Candiotti et al. A prospective, multicentre, randomized, double-blind, parallel-group study evaluated 157 children 2 to 16 years of age undergoing elective surgery. Total control of postoperative nausea and vomiting during the first 2 hours after surgery was observed in most patients.

5.2 Pharmacokinetic properties

Pharmacokinetics of the oral administration is linear up to 2.5-fold of the recommended dose in adults. It is clear from the extensive dose-finding programme that the antiemetic efficacy is not unequivocally correlated with either administered doses or plasma concentrations of granisetron.
A fourfold increase in the initial prophylactic dose of granisetron made no difference in terms of either the proportion of patient responding to treatment or in the duration of symptoms control.

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

Biotransformation
Granisetron is metabolized primarily in the liver by oxidation followed by conjugation. The major compounds are 7-OH-granisetron and its sulphate and glycuronide conjugates. Although antiemetic properties have been observed for 7-OH-granisetron and indazoline N-desmethyl granisetron, it is unlikely that these contribute significantly to the pharmacological activity of granisetron in man. *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 (see section 4.5).

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 faeces as metabolites. Mean plasma half-life in patients by the oral and intravenous route is approximately 9 hours, with a wide inter-subject variability.

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 neoplasic 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 (see section 4.2).

Elderly patients
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 are similar to those in adults when appropriate parameters (volume of distribution, total plasma clearance) are normalized for body weight.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, reproductive toxicity and genotoxicity. Carcinogenicity studies revealed no special hazard for humans when used in the recommended human dose. However, when administered in higher doses and over a prolonged period of time the risk of carcinogenicity cannot be ruled out.

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. 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 the ECG trace. If changes do occur, they are generally without clinical significance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Citric acid monohydrate
Water for injection
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

Unopened: 2 years
Once opened, use immediately. For single use only. Discard any remaining portion.

6.4 Special precautions for storage

Do not store above 30^{o}C. Keep the ampoules in the outer carton in order to protect from light. Do not freeze.

6.5 Nature and contents of container

Granisetron Martindale Pharma is filled in clear 1ml Type I glass ampoules supplied in packs of ten ampoules in an outer carton.

6.6 Special precautions for disposal and other handling

Dilute before use. For single use only. Discard any unused contents appropriately.

Preparing the infusion
Children: To prepare the dose of 40 µg/kg, the appropriate volume is withdrawn and diluted with infusion fluid to a total volume of 10 to 30 ml. Any one of the following solutions may be used: 0.9% w/v Sodium Chloride Injection; 0.18% w/v Sodium Chloride and 4% w/v Glucose Injection; 5% w/v Glucose Injection; Hartmann's Solution for Injection; Sodium Lactate Injection; or 10% Mannitol Injection. No other diluents should be used.

Preparing the slow intravenous injection
Adults: A single dose of 1 mg of Granisetron Martindale Pharma should be diluted to 5 ml and administered as a slow intravenous injection (over 30 seconds).
Ideally, intravenous infusions of Granisetron Martindale Pharma should be prepared at the time of administration. After dilution (see above), or when the container is opened for the first time, the shelf-life is 24 hours when stored at ambient temperature in normal indoor illumination protected from direct sunlight. It must not be used after 24 hours. If to be stored after preparation, Granisetron Martindale Pharma infusions must be prepared under appropriate aseptic conditions. The product does not contain a preservative. Any unused portion should be discarded.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 0361/029/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 5th September 2008.

10 DATE OF REVISION OF THE TEXT

February 2014