IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0711/121/001
Case No: 2029298

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Rowex Ltd

Bantry, **Co. Cork**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Granetron 1 mg/ml. concentrate for solution for infusion or injection

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **14/11/2008** until **13/11/2013**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Granetron 1 mg/1 ml concentrate for solution for infusion or injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial with 1 ml concentrate for solution for injection or infusion contains granisetron hydrochloride equivalent to 1 mg granisetron.

Each vial with 3 ml concentrate for solution for injection or infusion contains granisetron hydrochloride equivalent to 3 mg granisetron.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for injection or infusion.

A clear, colourless to slightly yellow solution pH between 4.0 and 6.0.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prevention or treatment of acute nausea and vomiting induced by cytostatic therapy (chemotherapy or radiotherapy).

Additional indication for granisetron 1mg vials:
Prevention and treatment of post-operative nausea and vomiting.

4.2 Posology and method of administration

Cytostatic therapy

Adults
For prevention or treatment of nausea and vomiting induced by cytostatic therapy a single dose of 1 mg granisetron is recommended. In some patients a single dose of 3 mg may be preferable.
For prevention or treatment of nausea and vomiting induced by radiotherapy a single dose of 3 mg granisetron is recommended.

Granetron 1mg/ml. concentrate for solution for infusion or injection is for intravenous administration only. Granisetron 1 mg or 3 mg should be administered *either* in 5 ml or 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: In clinical trials, 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 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.

Children (aged 2 years and over) and adolescents
Prevention: A single dose of 40 μg/kg bodyweight is recommended in children with a body weight up to 25 kg. In children with a body weight ≥ 25 kg a single dose of 1 mg granisetron is recommended, In some patients a single dose of 3 mg may be preferable. Granisetron 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 μg/kg bodyweight (up to 3 mg) may be administered within a 24-hour period if required. This additional dose should be administered at least 10 minutes apart from the initial infusion.

Children under 2 years of age:
Granisetron should not be used because there are no sufficient data in children under 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.

Post-operative nausea and vomiting
Applicable for granisetron 1mg vials only (see section 4.1)

Adults
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 anaesthesia.
For the treatment of established post-operative 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.

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

Elderly
As for adults.

Patients with renal or hepatic impairment
As for adults.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

As granisetron may reduce lower bowel motility, patients with signs of sub-acute intestinal obstruction should be monitored following administration of granisetron.
No special precautions are required for the elderly or renally or hepatically impaired patient.

5-HT3 antagonist, 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.

There is no experience in children younger than two years old.

This medicinal product contains 1.4 mmol (or 31.5 mg) sodium per maximum daily dosage (9 mg granisetron). To be taken into consideration by patients on a controlled sodium diet.'.

4.5 Interaction with other medicinal products and other forms of interaction

Animal studies indicate that granisetron neither stimulates nor inhibits the cytochrome P450 enzyme system.

Because granisetron is metabolised by hepatic cytochrome P-450 drug-metabolising enzymes, inducers or inhibitors of these enzymes may change clearance and, hence the half-life of granisetron.

In human subjects, hepatic enzyme induction by phenobarbital has led to an increase in total plasma clearance (approximately 25 %) following intravenous administration of granisetron.

To date no signs of interaction have been observed between granisetron and medicinal products that are often prescribed in anti-emetic therapy, such as benzodiazepines, neuroleptics and drugs for peptic indications. Furthermore, no interaction has been observed between granisetron and emetogenic cytostatic therapies.

No specific interaction studies have been conducted in anaesthetised patients, but granisetron has been safely administered with commonly used anaesthetic and analgesic agents.

In vitro studies have shown that ketoconazole may inhibit the metabolism of granisetron via the cytochrome P450 3A isoenzyme family. The clinical significance of this is unknown.

4.6 Pregnancy and lactation

Pregnancy
There are no data from the use of granisetron in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Granisetron should not be used in pregnant women unless strictly indicated.

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

There has been no evidence from human studies that granisetron has any adverse effect on alertness.

4.8 Undesirable effects

In this section undesirable effects are defined 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), not known (cannot be estimated from the available data).

Cardiac disorders
Rare: Arrhythmia, chest pain

Nervous system disorders
Very common: Headache
Very rare: Fainting fits, coma, extrapyramidal disorder, dizziness

Gastrointestinal disorders
Very common: Constipation, nausea
Common: Diarrhoea, vomiting, abdominal pain

Skin and subcutaneous tissue disorders
Very rare: Rash

Metabolism and nutrition disorders
Common: Reduced appetite
Very rare: Anorexia

General disorders and administration site conditions
Common: Asthenia, pain, fever

Immune system disorders
Very rare: Anaphylaxis

Hepatobiliary disorders
Rare: Abnormal hepatic function, raised transaminase levels

Psychiatric disorders
Very rare: Insomnia, agitation

4.9 Overdose

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Granisetron is a potent anti-emetic and highly selective antagonist of 5-hydroxytryptamine ($5\text{-}HT_3$) receptors. Radioligand binding studies have demonstrated that granisetron has negligible affinity for other receptor types including 5-HT and dopamine D_2 binding sites.
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-irradiation.
Granisetron is effective, intravenously, in the prevention and treatment of post-operative nausea and vomiting.

5.2 Pharmacokinetic properties

General characteristics

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 dose whilst that of metabolites amounts to about 47% of dose. The remainder is excreted in 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 anti-emetic 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 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.

Regarding safety pharmacology, 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

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

6.2 Incompatibilities

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

Prophylactic administration of Granisetron 1mg/ml. concentrate for solution for infusion or injection should be completed prior to the start of cytostatic therapy or induction of anesthesia

6.3 Shelf Life

2 years

After dilution: Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the product should be used immediately.

6.4 Special precautions for storage

Keep the vial in the outer carton in order to protect from light.

Do not freeze.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

- 2 ml clear type I glass vial with a 13 mm rubber stopper and an aluminium seal with a dark blue flip-off button (for 1 ml of concentrate for solution for injection or infusion)
- 5 ml clear type I glass vial with a 13 mm rubber stopper and an aluminium seal with a dark blue flip-off button (for 3 ml of concentrate for solution for injection or infusion)
- 6 ml clear type I glass vial with a 20 mm rubber stopper and an aluminium seal with a dark blue flip-off button (for 3 ml of concentrate for solution for injection or infusion)

Pack sizes:
1 ml of concentrate for solution for injection or infusion: 1 and 5 vials.
3 ml of concentrate for solution for injection or infusion: 1 and 5 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Dilute before use. For single use only. Any unused portion should be discarded.
Intravenous injections and infusions of Granetron 1mg/ml. concentrate for solution for infusion or injection should be prepared at the time of administration and used immediately from a microbiological point of view. In-use storage times and conditions prior to use are not supported by microbiological data and are the responsibility of the user, Granetron 1mg/ml. concentrate for solution for infusion or injection (see section 6.3).

The diluted injections and infusions are to be inspected visually for particulate matter prior to administration. They should only be used if the solution is clear and free from particles.

Preparing the injection

Adults: To prepare a dose of 1 mg, 1 ml is withdrawn from the vial and diluted to 5 ml with 0.9% w/v Sodium Chloride Injection BP.
To prepare a dose of 3 mg, 3 ml is withdrawn from the vial and diluted to 15 ml with 0.9% w/v Sodium Chloride Injection BP (for bolus administration)

Preparing the infusion

Adults: To prepare a dose of 1 mg or 3 mg, 1 ml or 3 ml is withdrawn from the vial and diluted in infusion fluid to a total volume of 20 to 50 ml in any of the following solutions: 0.9% w/v Sodium Chloride Injection BP; 0.18% w/v Sodium Chloride and 4% w/v Glucose Injection BP; 5% w/v Glucose Injection BP; Hartmann's Solution for Injection BP; Sodium Lactate Injection BP; or 10% Mannitol Injection BP. No other diluents should be used.

Children: To prepare the dose of 40 μg/kg the appropriate volume (up to 3 ml) is withdrawn from the vial and diluted with infusion fluid (as for adults) to a total volume of 10 to 30 ml.

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

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd.
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA711/121/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 14th November 2008

10 DATE OF REVISION OF THE TEXT