IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0736/028/001
Case No: 2036667

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

B. Braun Melsungen AG

Carl-Braun Strasse 1, **34212 Melsungen**, **Germany**

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

Granisetron B. Braun 1mg/ml concentrate for solution for injection or infusion.

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 **01/08/2008** until **31/07/2013**.

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

Granisetron B. Braun 1mg/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.
Clear, colourless solution with a pH adjusted to 5 (nominal range : 4-6) and osmolality is 318 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Granisetron B.Braun 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 B.Braun is for intravenous administration only.

Adults
The dose can be administered as an intravenous bolus over not less than 30 seconds diluted with 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 B. Braun can also be diluted in 20 to 50 ml infusion fluid and then administered over 5 minutes.

For further instructions regarding preparation see section 6.6.

Prevention
The recommended dose of Granisetron B.Braun is 1 mg or 3 mg depending on the emetogenic potential of the chemotherapy or radiotherapy. In clinical trials, the majority of patients have required only a single dose of Granisetron B.Braun 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 B.Braun should be completed prior to the start of cytostatic therapy.

Treatment
The same dose of Granisetron B.Braun 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 B.Braun may be administered within a 24-hour period. The maximum dose of Granisetron B.Braun 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 B.Braun of 20 – 40 µg/kg body weight (up to 3 mg) should be administered by intravenous infusion, diluted in10 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 B.Braun as above should be used for treatment as 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 B.Braun 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 B.Braun (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 B.Braun 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-HT_3 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 B.Braun in human pregnancy. Therefore Granisetron B.Braun 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 B.Braun 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 B.Braun he/she should be advised not to drive, not to operate machinery and not to carry out any work that requires 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	≥1/10
Common	≥1/100, <1/10
Uncommon	≥1/1.000, <1/100
Rare	≥1/10.000, <1/1.000
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	Rare: arrhythmias such as sinus bradycardia, atrial fibrillation, varying degrees of AV-block, ventricular ectopy (including non-sustained tachycardia), ECG abnormalities

Nervous system disorders	Very common: headache Common: somnolence, agitation, anxiety, insomnia, taste disorder Rare: dystonia and dyskinesia have been reported with medicines in the 5-HT3 antagonist class
Eye disorders	Uncommon: abnormal vision
Ear and labyrinth disorders	Common: dizziness
Gastrointestinal disorders	Common: diarrhoea, constipation, anorexia
Skin and subcutaneous tissue disorders	Uncommon: skin rashes Rare: local irritations at administration site after repeated intravenous administration
Vascular disorders	Common: hypertension Rare: hypotension
General disorders	Common: fever, asthenia
Immune system disorders	Rare: hypersensitivity reactions, sometimes severe (e.g., anaphylaxis, shortness of breath, hypotension, urticaria) Very rare: oedema (including facial oedema)
Hepatobiliary disorders	Rare: abnormal hepatic function, raised transaminase levels

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-HT_3) antagonists (A04AA02)

Granisetron B.Braun is a potent anti-emetic and highly selective antagonist of 5-hydroxytryptamine (5 HT_3) receptors.

Radioligand binding studies have demonstrated that Granisetron B.Braun has negligible affinity for other receptor types including 5 HT and dopamine D2 binding sites.

Granisetron B.Braun 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.

5.2 Pharmacokinetic properties

Absorption
Following intravenous doses in the range of 20-160 mcg/kg, plasma pharmacokinetics (Cmax 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 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 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 injection

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 and other handling

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 B.Braun 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 hydrogencarbonate injection
2.74% w/v sodium hydrogencarbonate injection
4.2% w/v sodium hydrogencarbonate 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 B.Braun 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

B. Braun Melsungen AG
Carl-Braun Strasse 1
34212 Melsungen
Germany

8 MARKETING AUTHORISATION NUMBER

PA736/28/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: August 1st 2008

10 DATE OF REVISION OF THE TEXT