IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA1380/001/002
Case No: 2057606

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

Actavis Group PTC ehf

Reykjavikurvegi 76-78, **220 Hafnarfjordur**, **Iceland**

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

Granisetron 3 mg/3 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 **20/01/2009** until **02/10/2013**.

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 3 mg/3 ml Concentrate For Solution For Infusion Or Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml concentrate for solution for infusion or injection contains 1 mg granisetron (as granisetron hydrochloride).

One 3 ml ampoule contains 3 mg granisetron (as granisetron hydrochloride).

Excipient(s): Sodium chloride 9 mg/ml (equivalent to 3.54 mg sodium/ml)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion/injection

Clear, colourless or slightly straw-coloured solution in a clear glass ampoule. pH 4.7-8.0

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Granisetron 3 mg/3 ml concentrate for solution for infusion or injection is indicated for the prevention and treatment of nausea and vomiting associated with cytostatic therapy and for the prevention and treatment of post-operative nausea and vomiting.

4.2 Posology and method of administration

For intravenous administration only as infusion or bolus injection.

Prevention and treatment of nausea and vomiting associated with cytostatic therapy:
Adults:
3 mg (3 ml) should be administered *either* in 15 ml infusion fluid as an intravenous bolus injection (30 sec.) *or* diluted in 20 ml to 50 ml solution for infusion as I.V. infusion over 5 minutes immediately prior to chemotherapy. The treatment may be repeated twice during the subsequent 24 hours. At least 10 minutes should elapse between repeated treatments.

Children (2 to 16 years of age):

A single dose of 20 µg/kg body weight is administered as an intravenous infusion, diluted in 10 to 30 ml solution for infusion and administered over five minutes. Administration should be completed before cytostatic therapy is initiated.

If required, one additional dose of 20 µg/kg body weight can be administered within 24-hours .The interval between repeated treatments should be at least 10 minutes.

Prevention and treatment of post-operative nausea and vomiting
Adults:
1 mg (1 ml) should be diluted to 5 ml and administered as a slow intravenous injection (30 sec) prior to anaesthesia. The treatment may be repeated once during the subsequent 24 hours.

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

Children:
There is no experience with the use of Granisetron 1 mg/ ml Concentrate For Solution For Infusion Or Injection for prevention and treatment of post-operative nausea and vomiting in children. Therefore, Granisetron 1 mg/ ml Concentrate For Solution For Infusion Or Injection cannot be recommended for the treatment of post-operative nausea and vomiting in this age group.

Elderly

As in adults.

Impaired renal function

No special requirements.

Impaired hepatic function

Granisetron 3 mg/3 ml concentrate for solution for infusion or injection should be used with caution in patients with impaired hepatic function.

4.3 Contraindications

Hypersensivity to granisetron and 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 closely following administration of granisetron.
The effect of granisetron may be increased by concomitant administration of dexamethasone or other glucocorticoids.

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 less than 1 mmol sodium (23 mg) per dose, i.e. essentially “sodium free.

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 metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes, inducers or inhibitors of these enzymes may change the 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 (approx. 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.

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:
Studies in a limited number of exposed pregnant women indicate no adverse effects of granisetron on pregnancy or on the health of the foetus/newborn child. To date no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Granisetron should not be used in pregnant women unless strictly indicated and caution should be exercised when prescribing to pregnant women.

Lactation:
As there are no data on the excretion of granisetron in breast milk, breast feeding should be discontinued during therapy.

4.7 Effects on ability to drive and use machines

There is no information available on any adverse effect of granisetron on the ability to drive or to operate machinery

4.8 Undesirable effects

Cardiac disorders Rare (>1/10 000, <1/1 000):	Arrhythmia, chest pain
Nervous system disorders Very common (≥1/10) Very rare (<1/10.000), not known (cannot be estimated from the available data)	Headache Coma, extrapyramidal disorders
Gastrointestinal disorders Very common (≥1/10) Common (≥1/100 and <1/10)	Nausea, constipation Reduced appetite, diarrhoea, vomiting, abdominal pain
Skin and subcutaneous tissue disorders Very rare (<1/10.000), not known (cannot be estimated from the available data))	Rash
General disorders and administration site conditions Common (≥1/100 and <1/10) Very rare (<10.000), not known (cannot be estimated from the available data))	Asthenia, pain, fever Anaphylaxy, fainting, dizziness, insomnia, agitation
Hepatobiliary disorders Rare – very rare (<1/1.000)	Abnormal hepatic function, increased transaminases
Psychiatric disorders Very rare (<1/10.000), not known (cannot be estimated from the available data)	Anorexia

4.9 Overdose

Overdosage of up to 38.5 mg granisetron hydrochloride administered as parenteral single dose, has been reported without symptoms or with mild headache only.

Symptoms:
Blurred vision, diplopia, dizziness, headache, fatigue, tachycardia, bradycardia, hypotension, dystonia, muscle spasm, restlessness, agitation, hallucinations and seizures.

Treatment:
There is no antidote for granisetron. In case of overdosage, symptomatic treatment is given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Serotonin (5HT3) antagonists,
ATC code: A04AA02.
Granisetron is a potent antiemetic and selective 5-hydroxytryptamine ($5 - HT_3$) receptor antagonist. Binding studies have demonstrated that granisetron has negligible affinity to other receptor types including 5 – HT and dopamine D_2 binding sites.

Granisetron prevents effectively nausea and vomiting caused by cytostatics or X-ray radiation of the whole body, both prophylactically and when these symptoms occur during treatment.

Granisetron has no influence on the plasma concentrations of prolactin or aldosterone.

5.2 Pharmacokinetic properties

General characteristics

Distribution:
Granisetron 3 mg/3 ml concentrate for solution for infusion or injection is distributed in most of the body with a mean volume of distribution of 3 L/kg; plasma protein binding is approximately 65 %.

Biotransformation:
Granisetron is biotransformed by N-demethylation and oxidation of the aromatic ring followed by conjugation.

Elimination:
Clearance is predominantly via hepatic metabolism. 12 % of the administered dose is excreted unchanged in urine and 47% as metabolites. The remaining metabolites are excreted in faeces. Mean plasma half-life in patients is approximately 9 hours, but with a wide intersubject variability.

The pharmacokinetics of granisetron remained linear at oral doses up to 2.5 times the recommended therapeutic dose.

Patient characteristics:
The plasma concentration of granisetron is not clearly correlated to the anti-emetic efficacy of the substance. Clinical benefit may be achieved even when granisetron is not detectable in plasma.

Following administration of one single intravenous dose in elderly, the pharmacokinetic parameters do not differ from similar parameters in younger individuals. In patients with severe renal insufficiency data indicate that the pharmacokinetic parameters are almost identical with similar parameters in healthy individuals. In patients with impaired hepatic function 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 dose adjustment is necessary.

Following a single intravenous dose in children the pharmacokinetic parameters (volume of distribution and plasma clearance) are on a par with the similar parameters for adults, calculated according to body weight.

5.3 Preclinical safety data

Data from two-year carcinogenicity studies have shown an increase in hepatocellular carcinoma and/or adenoma in rats and mice of both sexes given 50mg/kg (rat dosage reduced to 25mg/kg/day at week 59). Increases in hepatocellular neoplasia were also detected at 5mg/kg in male rats. In both species, drug-induced effects (hepatocellular neoplasia) were not observed in the low-dose group (1mg/kg).
In several *in vitro* and *in vivo* assays, granisetron was shown to be non-genotoxic in mammalian cells.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Hydrocloride acid for pH adjustment
Sodium hydroxide for pH adjustment
Water for injections

6.2 Incompatibilities

As general precaution, Granisetron 3 mg/3 ml concentrate for solution for infusion or injection should never be mixed in the same solution with other drugs except those mentioned in section 6.6. Prophylactic injection of Granisetron 3 mg/3 ml concentrate for solution for infusion or injection should be completed prior to initiation of cytostatic therapy or induction of anaesthesia.

6.3 Shelf Life

3 years.

After opening and dilution: 24 hours

Chemical and physical in-use stability has been demonstrated for 24 hours at 15-25^{o}C. 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 8^{o}C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened ampoule:

Store below 30^{o}C. Keep the ampoules in the outer carton in order to protect from light.

Diluted solution: Store in a refrigerator (2°C - 8°C) (see section 6.3)

6.5 Nature and contents of container

Granisetron 3 mg/3 ml concentrate for solution for infusion or injection is available in 3ml transparent glass ampoules (type I) in an outer carton

Pack sizes:
5 x 3 ml
1 x 3 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only. Any unused portion should be discarded

Adults: A dose of 1 mg is prepared by withdrawing 1 ml out of the ampoule and diluting to 5 ml with 9 mg/ml (0.9 %) sodium chloride for injection. No other solution should be used.

Children: To prepare a dose of 40 µg/kg the appropiate volume is withdrawn and diluted with solution for infusion to a total volume of between 10 and 30 ml. Any of the following solutions can be used:

9 mg/ml (0.9 %) Sodium chloride
1.8 mg/ml (0.18 %) Sodium chloride and 40 mg/ml (4 %) Glucose solution
50 mg/ml (5%) Glucose solution
Hartmann's solution for injection
Sodium lactate solution
100 mg/ml (10 %) Mannitol solution
No other diluents should be used.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf.

Reykjavikurvegi 76-78,

220 Hafnarfjordur

Iceland

8 MARKETING AUTHORISATION NUMBER

PA 1380/1/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 3rd October 2008

10 DATE OF REVISION OF THE TEXT

January 2009