**IRISH MEDICINES BOARD ACTS 1995 AND 2006**

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

**(S.I. No.540 of 2007)**

**PA0749/027/001**
Case No: 2062281

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

**Teva Pharma B.V.**

**Computerweg 10**, **3542 DR Utrecht**, **Netherlands**

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

**Granisetron Teva 1 mg Film-coated Tablets**

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 **01/09/2009**.

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 Teva 1 mg Film-coated Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1 mg granisetron as granisetron hydrochloride.

Excipients:
Each 1 mg tablet contains 64.88 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated tablet.
White to off white, film coated, capsule shaped tablet, debossed with “93” on one side of the tablet and with “7485” on the other side of the tablet.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Granisetron is used to prevent acute nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.

### 4.2 Posology and method of administration

***Adults and children over 12 years old weighing more than 50 kg:***
The dose of granisetron is one 1 mg tablet twice a day or one 2 mg tablet once a day, to be taken on the day of cytostatic therapy.

The (first) dose should be administered shortly before (within one hour before) the start of cytostatic therapy.

Since it is not possible to administer a dose of less than 1 mg of granisetron, the tablets are not suitable for children weighing less than 50 kg or under 12 years of age.

***Granisetron in combination with a corticosteroid:***
In some circumstances (e.g. use of highly emetic drugs or with high doses), concomitant use of corticotherapy enhances the efficacy of granisetron. The following regimen has been shown to be effective: intravenous administration of 8-20 mg dexamethasone prior to the start of administration of cytostatic therapy, or 250 mg methylprednisolone prior to the start of and after administration of cytostatic therapy.

***Maximum dose and duration of treatment***
The maximum oral dose that patients should be given is 9 mg in one day. There is clinical experience with patients being given a total of 28 mg in 14 days.

***Special patient groups:***
*Elderly:*
The same dose as for adults (see section 5.2).

*Renally and/or hepatically impaired patients:*

The same dose as for adults (see section 5.2).

## 4.3 Contraindications

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

## 4.4 Special warnings and precautions for use

Cross-hypersensitivity reactions have been reported in patients who received other selective 5-$HT_3$ receptor antagonists. Patients with a history of mild to severe hypersensitivity reactions to a 5-$HT_3$ antagonist should be closely monitored following the administration of granisetron.

As granisetron may reduce bowel motility, patients with signs of (sub-)acute intestinal obstruction should be monitored following administration of granisetron.

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 lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## 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 P450 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***
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/fetal development, parturition or postnatal development. Granisetron should not be used in pregnant women unless strictly indicated. Caution should be exercised when prescribing granisetron to pregnant women.

***Lactation***
There are no data concerning granisetron excretion in breast milk. Therefore, breast-feeding should be discontinued during therapy.

## 4.7 Effects on ability to drive and use machines

There are no known data on the effect of granisetron on the ability to drive. In clinical studies occasional cases of drowsiness have been reported, but no causal connection with the use of granisetron has been demonstrated.

## 4.8 Undesirable effects

The adverse events are classified according to the following frequency categories: very common (≥1/10), common (≥ 1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10 000, < 1/1000), very rare (≤1/10 000).

| | |
|---|---|
| ***Psychiatric disorders*** | |
| *Very rare* | Anorexia |
| ***Nervous system disorders*** | |
| *Very common* | Headache |
| *Very rare* | Coma, extrapyramidal disorder |
| ***Gastrointestinal disorders*** | |
| *Very common* | Nausea, constipation |
| *Common* | Reduced appetite, diarrhoea, vomiting, abdominal pain |
| ***Skin and subcutaneous tissue disorders*** | |
| *Very rare* | Rash |
| ***General disorders*** | |
| *Common* | Asthenia, pain, fever |
| *Very rare* | Anaphylaxis, fainting fits, dizziness, insomnia, agitation |
| ***Cardiac disorders*** | |
| *Rare* | Arrhythmia, chest pain |
| ***Hepatobiliary disorders*** | |
| *Rare* | Abnormal hepatic function, raised transaminase levels |

## 4.9 Overdose

There is no specific antidote. In the event of overdosage, symptomatic treatment should be given. There have been no known cases of overdosage with granisetron tablets.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Serotonin ($5HT_3$) antagonists
ATC code: A04A A02

Granisetron is a potent anti-emetic and highly selective antagonist of 5-hydroxytryptamine ($5\text{-}HT_3$) receptors. Pharmacological studies have demonstrated that granisetron is effective against nausea and vomiting as a result of cytotoxic chemotherapy and radiotherapy. Radioligand binding studies have demonstrated that granisetron has negligible affinity for other receptor types including $5\text{-}HT_1$, $5\text{-}HT_2$, $5\text{-}HT_4$ and dopamine $D_2$ binding sites.

## 5.2 Pharmacokinetic properties

***Absorption***
Absorption of granisetron is rapid and complete. Maximal plasma concentrations are observed after approximately 2 h. Bioavailability is reduced to about 60% as a result of first pass metabolism. Biovailability is not generally influenced by food. The pharmacokinetics of granisetron remained linear at oral doses up to 2.5 times the recommended therapeutic dose.

***Distribution***
Granisetron is distributed with a mean volume of distribution of approximately 3 l/kg; plasma protein binding is approximately 65%. The mean plasma clearance in patients is approximately 27 l/h and the mean plasma half-life is about 9 hours, with wide inter-subject variability. 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.

***Metabolism***
Biotransformation pathways involve *N*-demethylation and aromatic ring oxidation followed by conjugation.

***Elimination***
Granisetron clearance is primarily by metabolism. Urinary excretion of unchanged granisetron averages 12% of dose. Urinary excretion of metabolites amounts to about 47% of dose, with the remainder being excreted in faeces as metabolites.

***Pharmacokinetics in special populations***
In elderly subjects after single intravenous doses, pharmacokinetic parameters were within the range found for non-elderly subjects. In patients with severe renal failure, studies have shown that pharmacokinetic parameters after a single intravenous dose are generally similar to those in healthy subjects. In patients with hepatic impairment due to neoplastic liver involvement, total plasma clearance of an intravenous dose was approximately halved compared with patients without hepatic impairment. However, no dosage adjustment is necessary. When volume of distribution and total clearance are adjusted for body weight, the pharmacokinetics of granisetron after single intravenous dose is similar in paediatric and adult cancer patients.

## 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. 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

Core
Lactose monohydrate
Hypromellose (E464)
Microcrystalline cellulose
Sodium starch glycollate
Magnesium stearate (E572)
Coating
Titanium dioxide (E171)

Hypromellose (E464)
Polysorbate 80
Macrogol 400

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf Life

2 years

## 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

## 6.5 Nature and contents of container

Transparent and white opaque PVC/PVdC aluminium blisters.

Pack sizes:
1, 2, 5, 6, 10, 14, 50 and 100 film-coated tablets.
Hospital packs of 50 x 1, 10 x 1 and 100 x 1 film-coated tablets.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

No special requirements.

# 7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10,
3542 DR Utrecht
The Netherlands

# 8 MARKETING AUTHORISATION NUMBER

PA 749/27/1

# 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd November 2007

Date of last renewal: 1st September 2009

# 10 DATE OF REVISION OF THE TEXT

November 2009