Public Assessment Report

Decentralised Procedure

Granisetron 1mg Film-coated Tablets
Granisetron 2mg Film-coated Tablets

UK/H/0902/001-2/DC
UK licence no: PL 00289/0960-1

TEVA UK Ltd
LAY SUMMARY

On 20 February 2008, the MHRA granted TEVA UK Ltd Marketing Authorisations (licences) for the medicinal products Granisetron 1mg Film-coated Tablets (PL 00289/0960) and Granisetron 2mg Film-coated Tablets (PL 00289/0961). These are prescription only medicines (POM) for the prevention or treatment of nausea and vomiting. They may also be used to prevent nausea and vomiting after certain types of treatment such as chemotherapy or radiotherapy.

The active ingredient, granisetron, is an anti-emetic which blocks serotonin receptors in the gastro-intestinal tract and in the central nervous system.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Granisetron 1mg and 2mg Film-coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.
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## Module 1

**Information About Initial Procedure**

| Product Name          | Granisetron 1mg Film-coated Tablets  
<table>
<thead>
<tr>
<th></th>
<th>Granisetron 2mg Film-coated Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Application</td>
<td>Article 10.1, Generic Application</td>
</tr>
<tr>
<td>Active Substance</td>
<td>Granisetron</td>
</tr>
<tr>
<td>Form</td>
<td>Film-coated Tablet</td>
</tr>
<tr>
<td>Strength</td>
<td>1mg and 2mg</td>
</tr>
</tbody>
</table>
| MA Holder             | TEVA UK Ltd  
|                       | Brampton Road  
|                       | Hampden Park  
|                       | Eastbourne  
|                       | East Sussex  
|                       | BN22 9AG                             |
| Reference Member State| United Kingdom                      |
| Concerned Member States| 1mg: Austria, Belgium, Czech Republic, Germany, Denmark, Estonia, Spain, Finland, France, Hungary, Ireland, Italy, Lithuania, Luxembourg, Latvia, Netherlands, Portugal, Sweden, Slovenia and Slovakia  
|                       | 2mg: Austria, Belgium, Czech Republic, Germany, Denmark, Estonia, Finland, France, Hungary, Ireland, Italy, Lithuania, Luxembourg, Latvia, Netherlands, Portugal, Sweden, Slovenia and Slovakia |
| Procedure Number      | UK/H/0902/001-2/DC                  |
| Timetable             | Day 205 – 14 May 2007               |
Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Granisetron 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.
1 mg: 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-HT3 receptor antagonists. Patients with a history of mild to severe hypersensitivity reactions to a 5-HT3 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-HT3 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 \((\geq 1/10)\), common \((\geq 1/100, <1/10)\), uncommon \((\geq 1/1000, <1/100)\), rare \((\geq 1/10 \, 000, <1/1000)\), very rare \((\leq 1/10 \, 000)\).

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very rare</strong></td>
<td>Anorexia</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Very common</strong></td>
<td>Headache</td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>Coma, extrapyramidal disorder</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Very common</strong></td>
<td>Nausea, constipation</td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Reduced appetite, diarrhoea, vomiting, abdominal pain</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
</tr>
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<td>Rash</td>
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<td><strong>Common</strong></td>
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<td><strong>Very rare</strong></td>
<td>Anaphylaxis, fainting fits, dizziness, insomnia, agitation</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Rare</td>
</tr>
<tr>
<td>-------------------</td>
<td>------</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Rare</td>
</tr>
</tbody>
</table>

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 (5HT₃) antagonists
ATC code: A04A A02
Granisetron is a potent anti-emetic and highly selective antagonist of 5-hydroxytryptamine (5-HT₃) 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-HT₁, 5-HT₂, 5-HT₄ and dopamine D₂ 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. Bioavailability 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
- Hypermellose (E464)
- Microcrystalline cellulose
- Sodium starch glycollate
- Magnesium stearate (E572)

Coating
- Titanium dioxide (E171)
- Hypermellose (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 mg: 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 UK Limited
Brampton Road,
Hampden Park,
Eastbourne, East Sussex,
BN22 9AG

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/0960

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/02/2008

10 DATE OF REVISION OF THE TEXT
20/02/2008
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Granisetron 2 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 2 mg granisetron as granisetron hydrochloride.
Excipients:
Each 2 mg tablet contains 129.76 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
2 mg: White to off white, film coated, capsule shaped tablet, scored and debossed with “G2” on the left side of the score and smooth on the right side of the score. The other side of the tablet is smooth. The scoreline is only to facilitate breaking for ease of swallowing and not to divide the tablet into equal doses.

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.
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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).

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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-HT3 receptor antagonists. Patients with a history of mild to severe hypersensitivity reactions to a 5-HT3 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-HT3 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).

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td>Anorexia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Headache</td>
</tr>
<tr>
<td>Very rare</td>
<td>Coma, extrapyramidal disorder</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Nausea, constipation</td>
</tr>
<tr>
<td>Common</td>
<td>Reduced appetite, diarrhoea, vomiting, abdominal pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td>Rash</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Asthenia, pain, fever</td>
</tr>
<tr>
<td>Very rare</td>
<td>Anaphylaxis, fainting fits, dizziness, insomnia, agitation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Arrhythmia, chest pain</td>
</tr>
<tr>
<td>------</td>
<td>-----------------------</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td>Abnormal hepatic function, raised transaminase levels</td>
</tr>
</tbody>
</table>

### 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 (5HT₃) antagonists

ATC code: A04A A02

Granisetron is a potent anti-emetic and highly selective antagonist of 5-hydroxytryptamine (5-HT₃) 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-HT₁, 5-HT₂, 5-HT₄ and dopamine D₂ 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. Bioavailability 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
Hyromellose (E464)
Microcrystalline cellulose
Sodium starch glycollate
Magnesium stearate (E572)

Coating
Titanium dioxide (E171)
Hyromellose (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:
2 mg: 1, 2, 5, 6, 10, 50 and 100 film-coated tablets.
Hospital packs of 50 x 1, 10 x 1 and 5 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 UK Limited
Brampton Road,
Hampden Park,
Eastbourne, East Sussex,
BN22 9AG

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/0961

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/02/2008

10 DATE OF REVISION OF THE TEXT
20/02/2008
Module 3
Patient Information Leaflet

1. WHAT GRANISETRON IS AND WHAT IT IS USED FOR

- Granisetron belongs to a group of drugs called 5-HT3 receptor antagonists, which prevent or treat nausea (feeling sick) and vomiting.
- Granisetron is used to prevent nausea and vomiting after certain types of treatment such as chemotherapy or radiotherapy.

2. BEFORE YOU TAKE GRANISETRON

Do NOT take Granisetron:
- If you are allergic (hypersensitive) to granisetron or any of the other ingredients of this medicine.

Take special care with Granisetron:
- If you are allergic (hypersensitive) to other 5-HT3 receptor antagonists, e.g. ondansetron.
- If you have problems with your bowels, e.g. severe constipation.
- If you have a painful or swollen abdomen.
- If you have heart rhythm disorders.
- If you have heart rhythm disorders.

Taking other medicines
You should tell your doctor if you are taking any of the following:
- Medicines to treat heart rhythm disorders.
- Beta-blockers as granisetron may affect the way your heart beats.
- Ketoconazole (an antifungal) and phenobarbital (an antiepileptic) may influence the way your body handles granisetron.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

Pregnancy
There is not enough information available on the use of Granisetron in pregnancy for the possible harmful effects to be evaluated. Granisetron must only be taken in pregnancy following consultation with your doctor. Tell your doctor if you are pregnant, think you are pregnant, or are intending to become pregnant.

Breast-feeding
It is not known whether Granisetron enters breast milk, and therefore, breast-feeding should be discontinued during therapy.

Driving and using machines
No studies on the effects of Granisetron on the ability to drive and use machines have been performed. Drowsiness was occasionally reported in clinical studies.

You should refrain from driving or using machines if you experience drowsiness.

Important information about some of the ingredients of Granisetron
Do not take Granisetron if you have been told by your doctor that you have an intolerance to some sugars, as these tablets contain lactose. If so, you should consult your doctor before taking this medicine.

3. HOW TO TAKE GRANISETRON

Always take Granisetron exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose is:
Adults and children over 12 years of age weighing more than 50 kg:
1 mg twice a day or 2 mg once a day on the day of chemotherapy or radiotherapy. The maximum dose of Granisetron should not exceed 9 mg in 24 hours.

The first tablet should be taken within 1 hour of the start of your chemotherapy or radiotherapy.

Children weighing less than 50 kg or under 12 years of age:
Granisetron is not recommended for children weighing less than 50 kg or under 12 years of age.

If you take more Granisetron than you should
If you (or someone else) swallow a lot of the tablets all together, or if you think a child has swallowed any of the tablets, contact your nearest hospital casualty department or your doctor immediately. Please take this leaflet, any remaining tablets and the container with you to the hospital or doctor so that they know which tablets were consumed.

If you forget to take Granisetron
If you forget to take a tablet, take one as soon as you remember, unless it is nearly time to take the next one. Never take two doses together. Take the remaining doses at the correct time.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Granisetron can cause side effects, although not everybody gets them.
If the following happens, tell your doctor immediately:
- An allergic reaction causing swelling of the face, lips, tongue or throat, difficulty breathing or swallowing, rash or itching.
This is a very serious but very rare side effect affecting fewer than one in every 10,000 patients treated. You may need urgent medical attention. Other allergic reactions such as minor skin rashes have also very rarely been reported.

The following side effects have been reported:
**Very common (affecting more than one person in 10):**
- Headache
- Nausea (feeling sick), constipation.

**Common (affecting fewer than one person in 10 but more than one person in 100):**
- Reduced appetite, diarrhoea, vomiting, abdominal pain
- Weakness, pain, fever.

**Rare (affecting fewer than one person in 1,000 but more than one person in 10,000):**
- Abnormal heart rhythm, chest pain
- Abnormal liver function.

If you are having blood tests to check how your liver is working, the results may be affected by this medicine.

**Very rare (affecting fewer than one person in 10,000):**
- Loss of appetite
- Coma, movement disorders such as abnormal gait
- Fainting, dizziness, insomnia, agitation.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**5 HOW TO STORE GRANISETRON**
- Keep out of the reach and sight of children.
- Do not use Granisetron after the expiry date that is stated on the outer packaging.
- This medicinal product does not require any special storage conditions.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

**6 FURTHER INFORMATION**

What Granisetron contains:
- The active ingredient is granisetron. The 1 mg film-coated tablets contain 1 mg granisetron as granisetron hydrochloride. The 2 mg film-coated tablets contain 2 mg granisetron as granisetron hydrochloride.
- The other ingredients are as follows:
  - Tablet core: lactose monohydrate, hypromellose (E464), microcrystalline cellulose, sodium starch glycolate, magnesium stearate (E472).
  - Film-coat: titanium dioxide (E171), polysorbate 80 and macrogol.

What Granisetron looks like and contents of the pack:
- Granisetron 1 mg Film-coated Tablets are white to off white, film coated, capsule shaped tablets, debossed with “93” on one side of the tablet and with “7485” on the other side of the tablet.
- Granisetron 2 mg Film-coated Tablets are white to off white, film coated, capsule shaped tablets, scored and debossed with “G2” on the left side of the score and smooth on the right side of the score. The other side of the tablet is smooth. The scoreline is only to facilitate breaking for ease of swallowing and not to divide the tablet into equal doses.

- The 1 mg tablets are available in pack sizes of 1, 2, 5, 6, 10, 14, 50 and 100 tablets. Hospital packs of 50 x 1, 10 x 1 and 100 x 1 tablets.
- The 2 mg tablets are available in pack sizes of 1, 2, 5, 6, 10, 50 and 100 tablets. Hospital packs of 50 x 1, 10 x 1 and 5 x 1 tablets.
- Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
- Marketing Authorisation holder and company responsible for manufacture:
  - TEVA UK Limited, Eastbourne, BN22 9AG.

Product Licence numbers:
- Granisetron 1 mg Film-coated Tablets:
  - PL 00289/0960
- Granisetron 2 mg Film-coated Tablets:
  - PL 00289/0961

This leaflet was last revised in May 2007.
Module 4
Labelling
Module 5

Scientific Discussion During Initial Procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products Granisetron 1mg Film-coated Tablets (PL 00289/0960) and Granisetron 2mg Film-coated Tablets (PL 00289/0961) on 20 February 2008. The products are prescription only medicines.

This application was made under Article 10.1 of 2001/83 EC, as amended, claiming that Granisetron 1mg and 2mg Film-coated Tablets are generic products of Kytril Tablets 1mg (SmithKline Beecham plc, trading as SmithKline Beecham Pharmaceuticals) authorised in January 1994 and Kytril Tablets (SmithKline Beecham plc, trading as Beecham Research, Bencard, Bridge Pharmaceuticals, SmithKline and French Laboratories, and SmithKline Beecham Pharmaceuticals) authorised in February 1996. A Change of Ownership was granted for both products (Kytril Tablets 1mg and 2mg) to Roche Products Ltd in September 2001. The reference products have therefore been authorised in the EEA for at least 10 years.

The products contain the active ingredient granisetron and are indicated for the prevention of acute nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.

Granisetron is an anti-emetic agent. It belongs to a class of specific 5HT3 antagonists which block 5HT3 receptors in the gastro-intestinal tract and in the central nervous system. These drugs are of value in the management of nausea and vomiting in patients receiving cytotoxics and in postoperative nausea and vomiting.

No new preclinical studies were conducted, which is acceptable given that the application referred to products that have been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application referred to products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of the product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

The decentralised procedure was completed at Day 205 (14 May 2007), with the RMS and the CMSs agreeing that the licences were approvable. The national phase of the decentralised procedure was completed in the UK on 20 February 2008.
## II ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Granisetron 1mg Film-coated Tablets  
Granisetron 2mg Film-coated Tablets |
| Name(s) of the active substance(s) (INN) | Granisetron |
| Pharmacotherapeutic classification (ATC code) | Serotonin (5HT3) antagonists (A04A A02) |
| Pharmaceutical form and strength(s) | 1mg and 2mg Film-coated Tablets |
| Reference number for the Decentralised Procedure | UK/H/0902/001-2/DC |
| Reference Member State | United Kingdom |
| Concerned Member States | 1mg: Austria, Belgium, Czech Republic, Germany,  
Denmark, Estonia, Spain, Finland, France, Hungary,  
Ireland, Italy, Lithuania, Luxembourg, Latvia,  
Netherlands, Portugal, Sweden, Slovenia and  
Slovakia  
2mg: Austria, Belgium, Czech Republic, Germany,  
Denmark, Estonia, Finland, France, Hungary,  
Ireland, Italy, Lithuania, Luxembourg, Latvia,  
Netherlands, Portugal, Sweden, Slovenia and  
Slovakia |
| Marketing Authorisation Number(s) | PL 00289/0960-1 |
| Name and address of the authorisation holder | TEVA UK Ltd  
Brampton Road  
Hampden Park  
Eastbourne  
East Sussex  
BN22 9AG |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

Granisetron Hydrochloride
Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification based on the European Pharmacopeia specification is provided for granisetron hydrochloride.

Analytical methods have been validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided for six batches and comply with the proposed specification.

Granisetron hydrochloride is stored in appropriate packaging.

Stability data have been generated which support a retest period of 60 months when stored in the proposed packaging at 25°C and 60% relative humidity.

DRUG PRODUCT

Other Ingredients
The excipients present are lactose monohydrate, hypromellose, microcrystalline cellulose, sodium starch glycollate and magnesium stearate. Titanium dioxide, hypromellose, polysorbate 80 and macrogol 400 are also present in the coating.

The excipients used comply with their respective European Pharmacopoiea monographs. Satisfactory certificates of analysis have been provided.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

Pharmaceutical Development
The applicant has provided suitable product development rationale and data.

Impurity Profile
Comparative impurity profiles for the reference product and test product are provided. The test product has a similar profile to the reference product.

Dissolution Profile
Comparative dissolution profiles were generated for the reference product and the test product showing that they have similar release profiles. The dissolution method used was chosen as it is the most discriminative.
Manufacture
Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. Suitable in-process controls are applied during the manufacturing process to ensure the quality of the product.

The manufacturing process has been validated and the results are satisfactory.

Control of Drug Product
The proposed finished product specifications are acceptable and provide an assurance of the quality of the finished products. The analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed specifications.

Reference Standards or Materials
Certificates of analysis for all reference standards used have been provided and are satisfactory.

Container Closure System
The finished product is packaged in transparent and white opaque PVC/PVdC aluminium blisters in pack sizes of 1, 2, 5, 6, 10, 50 and 100 film-coated tablets. Granisetron 1mg Film-coated Tablets are also available in a pack size of 14 tablets. Satisfactory specifications and certificates of analysis have been provided for the packaging components.

Stability of the Drug Product
The stability data provided support a shelf-life of 2 years, with no special storage conditions.

Bioequivalence/Bioavailability
Refer to the clinical assessment.

SPC, PIL, Labels
The SPC and labels are pharmaceutically acceptable.

The Patient Information Leaflet (PIL) is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act on the information that it contains.

CONCLUSION
It is recommended that Marketing Authorisations are granted for these applications.

III.2 NON-CLINICAL ASPECTS
No new non-clinical data have been supplied with these applications and none are required for applications of this type. The non-clinical overview gives an adequate update on the known pharmacological and toxicological properties of granisetron.
III.3 CLINICAL ASPECTS

CLINICAL PHARMACOLOGY

The applicant has submitted a bioavailability study involving 40 healthy subjects. This was an open label, single dose, randomised, two-period, two sequence, two treatment, crossover study comparing the bioavailability of Granisetron 2mg Film-coated Tablets (TEVA UK Ltd) and Kytril Tablets 2mg (Roche Products Ltd) under fasting conditions. Concentrations of granisetron were measured from the plasma samples collected over a 72-hour interval after doing in each period. There was a washout period of 7 days.

The pharmacokinetic parameters AUC_t, AUC_inf, C_max, T_max, K_el and T_half were estimated based on the granisetron plasma levels for each subject that was included in the statistical analysis.

Results:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Geometric Means</th>
<th>Arithmetic Means (CV%)</th>
<th>Ratio of Geometric Means (%)</th>
<th>90% Confidence Interval (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_t (ng*h/mL)</td>
<td>137.9579</td>
<td>143.0727</td>
<td>96.43</td>
<td>89.43 – 103.97</td>
</tr>
<tr>
<td>AUC_inf (ng*h/mL)</td>
<td>141.2263</td>
<td>146.2930</td>
<td>96.54</td>
<td>89.56 – 104.06</td>
</tr>
<tr>
<td>C_max (ng/mL)</td>
<td>10.3270</td>
<td>10.5653</td>
<td>97.74</td>
<td>91.74-104.15</td>
</tr>
<tr>
<td>T_max (h)</td>
<td>2.19 (49)</td>
<td>2.21 (41)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>T_half (h)</td>
<td>11.89 (34)</td>
<td>12.05 (32)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

The results of the study show that the 90% Confidence Intervals for the log-transformed parameters AUC and C_max for granisetron were all within the 80-125% acceptable range. These results therefore demonstrate that the test product, Granisetron 2mg Film-coated Tablets to be marketed by TEVA UK Ltd is bioequivalent to the reference product, Kytril Tablets 2mg marketed by Roche Products Ltd.

The essentially linear pharmacokinetics of granisetron, particularly at this relatively low dose range, makes it likely that the lower-dose granisetron formulation is also bioequivalent to the corresponding marketed brand formulation although bioequivalence has not been assessed explicitly.

Twenty-one and 25 adverse events were reported following treatments with the test and reference products respectively. These events occurred in 17 subjects and included constipation, loose stools, abdominal discomfort, headache, dizziness and nausea. Fourteen...
were assessed as unrelated and 31 as probably or possibly related to study medication. None of the events were clinically significant. No serious adverse events were reported.

EFFICACY
No new efficacy data have been provided and none are required for applications of this type. However, the applicant has provided an extensive review of clinical trials published in the literature confirming the efficacy and safety of granisetron in patients with Alzheimer’s disease.

SAFETY
No new safety data have been provided and none are required for applications of this type. However, the applicant has provided a literature safety review of granisetron. No new safety issues have been identified.

EXPERT REPORT
A satisfactory clinical expert report has been submitted, which has been written by an appropriately qualified medical doctor.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
This is satisfactory and consistent with the SPC for the reference product.

PATIENT INFORMATION LEAFLET (PIL)
This is satisfactory and consistent with the SPC.

LABELLING
These are satisfactory.

CONCLUSION
The application contains an adequate review of published clinical data and bioequivalence to the reference product has been shown. Approval is recommended from the clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Granisetron 1mg and 2mg Film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Granisetron 2mg Film-coated Tablets and Kytril Tablets 2mg (Roche Products Ltd). Given that linear kinetics apply between the 1mg and 2mg Film-coated Tablets, that proportional formulae for the tablets have been used, the method of manufacture is the same and that similar dissolution results have been shown for the two strengths, a separate bioequivalence study using the 1mg Film-coated Tablet is not considered necessary.

No new or unexpected safety concerns arose from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference products.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the reference products are interchangeable. Clinical experience with granisetron is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 6

Steps Taken After Initial Marketing Authorisation Grant

The following table gives details of a non-safety update that was made to the Marketing Authorisations for these products after they were first licensed. Details of this update are included in Annex 1 of this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>23/02/2012</td>
<td>Type IB variation</td>
<td>To update Sections 4.1, 4.2, 4.4-4.9 and 5.1-5.3 of the SmPC in line with an Article 30 referral. As a consequence, the PIL has been updated.</td>
<td>Approved 09/07/2012</td>
</tr>
</tbody>
</table>
Annex 1 - Assessment report for variation to amend the SmPCs and PILs for Granisetron 1mg Film-coated Tablets and Granisetron 2mg Film-coated Tablets in line with an Article 30 referral.

As these variations were classified as Type IB variations, no assessment report was produced during the assessment process.

Following approval of these variations on 9 July 2012 the following updated SmPCs and PILs have been incorporated into Marketing Authorisations for Granisetron 1mg Film-coated Tablets (PL 00289/0960) and Granisetron 2mg Film-coated Tablets (PL 00289/0961):
SUMMARIES OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Granisetron 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.
1 mg: 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 film-coated tablets are indicated in adults for the prevention and treatment of acute nausea and vomiting associated with chemotherapy and radiotherapy.

Granisetron film-coated tablets are indicated in adults for prevention of delayed nausea and vomiting associated with chemotherapy and radiotherapy.

4.2 Posology and method of administration

Posology
1 mg tablet twice a day or 2 mg once a day for up to one week following radiotherapy or chemotherapy.
The first dose of granisetron should be administered within 1 hour before the start of therapy. Dexamethasone has been used concomitantly at doses up to 20 mg once a day orally.

Paediatric population
The safety and efficacy of granisetron tablets in children have not yet been established. No data are available.

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 (see section 5.2).
Method of administration
The tablets should be swallowed whole with water.

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

4.4 Special warnings and precautions for use
As granisetron may reduce bowel motility, patients with signs of sub-acute intestinal obstruction should be monitored following administration of granisetron.

As for other 5-HT3 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-HT3 antagonists (e.g. dolasteron, ondansetron) has been reported.

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

Paediatric population
There is insufficient clinical evidence to recommend administration of these tablets to children.

4.5 Interaction with other medicinal products and other forms of interaction
As for other 5-HT3 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 interaction 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 sectin 5.3). As precautionary measure, it is preferable to avoid use of granisetron during pregnancy.

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

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

4.7 Effects on ability to drive and use machines
Granisetron has no or negligible influence on the ability to drive and use machines.

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

Tabulated list of adverse reactions
The following table of listed adverse reactions is derived from clinical trials and post-marketing data associated with granisetron and other 5-HT3 antagonists.

<table>
<thead>
<tr>
<th>Immune system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Hypersensitivity reactions, e.g. anaphylaxis, urticaria</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Extrapyramidal reactions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>QT prolongation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Diarrhoea</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatobiliary disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Elevated hepatic transaminases*</td>
</tr>
</tbody>
</table>
**Skin and subcutaneous tissue disorders**

<table>
<thead>
<tr>
<th>Uncommon</th>
<th>Rash</th>
</tr>
</thead>
</table>

*Occurred at a similar frequency in patients receiving comparator therapy

**Description of selected adverse reactions**
As for other 5-HT3 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. In the case of overdose with tablets, symptomatic treatment should be given. Doses of up to 38.5 mg of granisetron 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 (5HT₃) antagonists
ATC code: A04A A02

*Neurological mechanisms, serotonin-mediated nausea and vomiting*
Serotonin is the main neurotransmitter responsible for emesis after chemo- or radio-therapy. The 5-HT₃ 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 center 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-HT₃ receptors are located. The released serotonin activates vagal neurons via the 5-HT₃ 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-HT₃) receptors. Radioligand binding studies have demonstrated that granisetron has negligible affinity for other receptor types including 5-HT, and dopamine D₂ binding sites.

*Chemotherapy- and radiotherapy-induced nausea and vomiting*
Granisetron administered orally has been shown to prevent nausea and vomiting associated with cancer chemotherapy in adults.
**Post-operative nausea and vomiting**
Granisetron administered orally 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 ketoconazole 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-HT3 receptor 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).

**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.

**Absorption**
Absorption of granisetron is rapid and complete, though oral bioavailability is reduced to about 60% as a result of first pass metabolism. Oral bioavailability is not generally influenced by food.

**Distribution**
Granisetron is extensively distributed, with a mean volume of distribution of approximately 3 l/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 neoplastic liver involvement, total plasma clearance of an intravenous dose was approximately halved compared with patients without hepatic impairment. Despite these changes, no dosage adjustment is necessary (see section 4.2).

**Paediatric population**
These tablets are not recommended in children.

**Eldery patients**
In elderly subjects after single intravenous doses, pharmacokinetic parameters were within the range found for non-elderly subjects.

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. 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**

**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 mg: 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 AUTHORITY
TEVA UK Limited
Brampton Road,
Hampden Park,
Eastbourne, East Sussex,
BN22 9AG

8 MARKETING AUTHORITY NUMBER(S)
PL 00289/0960

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/02/2008

10 DATE OF REVISION OF THE TEXT
09/07/2012
1  **NAME OF THE MEDICINAL PRODUCT**
Granisetron 2 mg Film-coated Tablets

2  **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each film-coated tablet contains 2 mg granisetron as granisetron hydrochloride.
Excipients:
Each 2 mg tablet contains 129.76 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3  **PHARMACEUTICAL FORM**
Film-coated tablet.
2 mg: White to off white, film coated, capsule shaped tablet, scored and debossed with “G2” on the left side of the score and smooth on the right side of the score. The other side of the tablet is smooth. The scoreline is only to facilitate breaking for ease of swallowing and not to divide the tablet into equal doses.

4  **CLINICAL PARTICULARS**

4.1  **Therapeutic indications**
Granisetron film-coated tablets are indicated in adults for the prevention and treatment of acute nausea and vomiting associated with chemotherapy and radiotherapy.

Granisetron film-coated tablets are indicated in adults for prevention of delayed nausea and vomiting associated with chemotherapy and radiotherapy.

4.2  **Posology and method of administration**

**Posology**
1 mg tablet twice a day or 2 mg once a day for up to one week following radiotherapy or chemotherapy.
The first dose of granisetron should be administered within 1 hour before the start of therapy. Dexamethasone has been used concomitantly at doses up to 20 mg once a day orally.

**Paediatric population**
The safety and efficacy of granisetron tablets in children have not yet been established. No data are available.

**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 (see section 5.2).

**Method of administration**
The tablets should be swallowed whole with water.

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

4.4 Special warnings and precautions for use
As granisetron may reduce bowel motility, patients with signs of sub-acute intestinal obstruction should be monitored following administration of granisetron.

As for other 5-HT3 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-HT3 antagonists (e.g. dolasteron, ondansetron) has been reported.

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

Paediatric population
There is insufficient clinical evidence to recommend administration of these tablets to children.

4.5 Interaction with other medicinal products and other forms of interaction
As for other 5-HT3 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 interaction 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 sectin 5.3). As precautionary measure, it is preferable to avoid use of granisetron during pregnancy.

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

Fertility
In rats, granisetron had no harmful effects on reproductive performance or fertility.
4.7 **Effects on ability to drive and use machines**
Granisetron has no or negligible influence on the ability to drive and use machines.

4.8 **Undesirable effects**

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

**Tabulated list of adverse reactions**
The following table of listed adverse reactions is derived from clinical trials and post-marketing data associated with granisetron and other 5-HT3 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)
- **Not known**: (cannot be estimated from the available data)

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<thead>
<tr>
<th>Immune system disorders</th>
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<tbody>
<tr>
<td><strong>Uncommon</strong></td>
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<tr>
<td>Hypersensitivity reactions, e.g.</td>
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<tr>
<td>anaphylaxis, urticaria</td>
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<th>Psychiatric disorders</th>
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<tr>
<td><strong>Common</strong></td>
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<td>Insomnia</td>
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<tr>
<th>Nervous system disorders</th>
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<tr>
<td><strong>Very common</strong></td>
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<tr>
<td>Headache</td>
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<td><strong>Uncommon</strong></td>
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<td>Extrapyramidal reactions</td>
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<tr>
<th>Cardiac disorders</th>
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<tr>
<td><strong>Uncommon</strong></td>
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<td>QT prolongation</td>
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<tr>
<th>Gastrointestinal disorders</th>
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<tbody>
<tr>
<td><strong>Very common</strong></td>
</tr>
<tr>
<td>Constipation</td>
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<tr>
<td><strong>Common</strong></td>
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<tr>
<td>Diarrhoea</td>
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<tr>
<th>Hepatobiliary disorders</th>
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<tr>
<td><strong>Common</strong></td>
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<tr>
<td>Elevated hepatic transaminases*</td>
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<th>Skin and subcutaneous tissue disorders</th>
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Uncommon | Rash

*Occurred at a similar frequency in patients receiving comparator therapy

**Description of selected adverse reactions**
As for other 5-HT3 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. In the case of overdose with tablets, symptomatic treatment should be given. Doses of up to 38.5 mg of granisetron 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 (5HT₃) antagonists
ATC code: A04A A02

*Neurological mechanisms, serotonin-mediated nausea and vomiting*
Serotonin is the main neurotransmitter responsible for emesis after chemo- or radiotherapy. The 5-HT3 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 solitarius of the vomiting center 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-HT3 receptors are located. The released serotonin activates vagal neurons via the 5-HT3 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-HT₃) receptors. Radioligand binding studies have demonstrated that granisetron has negligible affinity for other receptor types including 5-HT, and dopamine D₂ binding sites.

*Chemotherapy- and radiotherapy-induced nausea and vomiting*
Granisetron administered orally has been shown to prevent nausea and vomiting associated with cancer chemotherapy in adults.

*Post-operative nausea and vomiting*
Granisetron administered orally 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 ketoconazole 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-HT3 receptor 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).

**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.

**Absorption**

Absorption of granisetron is rapid and complete, though oral bioavailability is reduced to about 60% as a result of first pass metabolism. Oral bioavailability is not generally influenced by food.

**Distribution**

Granisetron is extensively distributed, with a mean volume of distribution of approximately 3 l/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 glucuronide 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 neoplastic liver involvement, total plasma clearance of an intravenous dose was approximately halved compared with patients without hepatic impairment. Despite these changes, no dosage adjustment is necessary (see section 4.2).

**Paediatric population**
These tablets are not recommended in children.

**Eldery patients**
In elderly subjects after single intravenous doses, pharmacokinetic parameters were within the range found for non-elderly subjects.

### 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. 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

**Core**
- Lactose monohydrate
- Hypromellose (E464)
- Microcrystalline cellulose
- Sodium starch glycollate
- Magnesium stearate (E572)

**Coating**
- Titanium dioxide (E171)
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:
2 mg: 1, 2, 5, 6, 10, 50 and 100 film-coated tablets.
Hospital packs of 50 x 1, 10 x 1 and 5 x 1 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORITY
TEVA UK Limited
Brampton Road,
Hampden Park,
Eastbourne, East Sussex,
BN22 9AG

8 MARKETING AUTHORIZATION NUMBER(S)
PL 00289/0961

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
20/02/2008

10 DATE OF REVISION OF THE TEXT
09/07/2012
PATIENT INFORMATION LEAFLET

The following text is the approved Product Information Leaflet (PIL) text. No PIL mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the PIL mock-ups has been obtained.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Granisetron 1 mg Film-coated Tablets
Granisetron 2 mg Film-coated Tablets
Granisetron

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

IN THIS LEAFLET:
1. What Granisetron is and what it is used for
2. Before you take Granisetron
3. How to take Granisetron
4. Possible side effects
5. How to store Granisetron
6. Further information

1. What Granisetron is and what it is used for

- Granisetron belongs to a group of drugs called ‘5-HT3 receptor antagonists’ or ‘antiemetics’. These tablets are only for use in adults. - Granisetron is used to prevent or treat nausea and vomiting (feeling and being sick) caused by other medical treatments such as chemotherapy or radiotherapy for cancer.

2. Before you take Granisetron

Do not take Granisetron:

- If you are allergic (hypersensitive) to granisetron or any of the other ingredients of this medicine (listed in section 6 Further information and “Important information about some of the ingredients of granisetron film-coated tablets” below).

If you are not sure, talk to your doctor, nurse, or pharmacist before taking these tablets.

Take special care with Granisetron:

Check with your doctor, nurse or pharmacist before using these tablets, if you:
- are having problems with your bowel movements because of a blockage of your gut (intestines),
- have heart problems, are being treated for cancer with a medicine that is known to damage your heart or have problems with levels of salts, such as potassium, sodium or calcium, in your body (electrolyte abnormalities),
- are taking other ‘5-HT3 receptor antagonists’ medicines. These include dolasetron, ondansetron used like granisetron in the treatment and prevention of nausea and vomiting.
Children
Children should not take these tablets.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is because Granisetron can affect the way some medicines work. Also some other medicines can affect the way these tablets work.
In particular, tell your doctor, nurse or pharmacist if you are taking the following:
- medicines to treat an irregular heartbeat,
- other ‘5-HT3 receptor antagonist’ medicines such as dolasetron or ondansetron (see “Take special care with Granisetron” above)
- phenobarbital, a medicine used to treat epilepsy
- a medicine called ketoconazole used in the treatment of fungal infections
- the antibiotic erythromycin used to treat bacterial infections.

Pregnancy and breast-feeding
You should not take these tablets if you are pregnant, trying to get pregnant or are breastfeeding, unless your doctor has told you to.

Ask your doctor, nurse or pharmacist for advice before taking any medicine.

Driving and using machines
Granisetron has no or negligible affect on your ability to drive or use any tools or machines.

Important information about some of the ingredients of Granisetron
This medicine contains lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Granisetron
Always take Granisetron exactly as your doctor has told you. You should check with your doctor, nurse or pharmacist if you are not sure.

The dose of Granisetron varies from one patient to another. It depends on your age, weight, and whether you are being given the medicine to prevent, or treat, nausea and vomiting. The doctor will work out how much to give you.

Prevention of feeling or being sick
Your first dose of Granisetron will usually be given an hour before your radio- or chemotherapy. The dose will be either one or two 1 mg tablets or one 2 mg tablet once a day for up to a week after your radio- or chemotherapy.

Treatment of feeling or being sick
The dose will usually be either one or two 1 mg tablets or one 2 mg tablet once a day, but your doctor may decide to increase your dose to up to nine 1 mg tablets a day.

If you take more Granisetron than you should
If you think you have taken too many of the tablets talk to your doctor or nurse. The symptoms of overdose include mild headaches. You will be treated depending on your symptoms.

**If you forget to take Granisetron**
If you think you have forgotten to take your medicine speak to your doctor or nurse. Do not take a double dose to make up for a forgotten tablet.

**If you stop taking Granisetron**
Do not stop taking your medicine before the treatment is finished. If you do stop taking your medicine, your symptoms may return.

If you have any further questions on the use of this product, ask your doctor, nurse or pharmacist.

4. **Possible side effects**

Like all medicines, Granisetron can cause side effects, although not everybody gets them.

If you notice the following problem you must see a doctor straight away:
- Allergic reaction (anaphylaxis). The signs may include swelling of the throat, face, lips and mouth, difficulty in breathing or swallowing.

Other side effects that may be experienced while taking this medicine are:

*Very common (affects more than 1 user in 10)*:
- Headache
- Constipation. Your doctor will monitor your condition.

*Common (affects 1 to 10 users in 100)*:
- Diarrhoea,
- Problems sleeping (insomnia)
- 
- Changes in how your liver is working shown by blood tests.

*Uncommon (affects 1 to 10 users 1,000)*:
- Skin rashes or an allergic skin reaction or “nettle-rash” or “hives” (urticaria). The signs may include red, raised itchy bumps
- Changes in heartbeat (rhythm) and changes seen on ECG readings (electrical recordings of the heart)
- Abnormal involuntary movements, such as shaking, muscle rigidity and muscle contractions

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. **How to store Granisetron**

Keep out of the reach and sight of children.

Do not use Granisetron after the expiry date that is stated on the carton or blister pack.
This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What Granisetron contains:
- The active ingredient is granisetron. The 1 mg film-coated tablets contain 1 mg granisetron as granisetron hydrochloride. The 2 mg film-coated tablets contain 2 mg granisetron as granisetron hydrochloride.
- The other ingredients are as follows:
  Tablet core: lactose monohydrate, hypromellose (E464), microcrystalline cellulose, sodium starch glycolate, magnesium stearate (E572)
  Film-coat: titanium dioxide (E171), polysorbate 80 and macrogol.

What Granisetron looks like and contents of the pack:
- Granisetron 1 mg Film-coated Tablets are white to off white, film coated, capsule shaped tablets, debossed with “93” on one side of the tablet and with “7485” on the other side of the tablet
- Granisetron 2 mg Film-coated Tablets are white to off white, film coated, capsule shaped tablets, scored and debossed with “G2” on the left side of the score and smooth on the right side of the score. The other side of the tablet is smooth. The scoreline is only to facilitate breaking for ease of swallowing and not to divide the tablet into equal doses.
- The 1 mg tablets are available in pack sizes of 1, 2, 5, 6, 10, 14, 50 and 100 tablets. Hospital packs of 50 x 1, 10 x 1 and 100 x 1 tablets
- The 2 mg tablets are available in pack sizes of 1, 2, 5, 6, 10, 50 and 100 tablets. Hospital packs of 50 x 1, 10 x 1 and 5 x 1 tablets.
- Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
<To be completed nationally>

This medicinal product is authorised in the member states of the EEA under the following names:
<To be completed nationally>

This leaflet was last approved in [06/2012]