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 1 mg granisetron as granisetron hydrochloride.
Each film-coated tablet contains 2 mg granisetron as granisetron hydrochloride.

Excipients:
Each 1 mg tablet contains 30 mg lactose monohydrate.
Each 2 mg tablet contains 60 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Granisetron 1 mg: White to off-white film coated triangular shaped biconvex tablet debossed with “G1” on one side and plain on the other side.

Granisetron 2 mg: Pale yellow to yellow colour triangular shaped biconvex film coated tablet debossed with “104” on one side and logo on other side.

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**

The dose of Granisetron is one 1 mg twice a day or 2 mg once a day for up to one week following radiotherapy or chemotherapy. The first dose of granisetron tablets 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.

**Special patient groups:**

**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 the active substance or to any of the excipients.

### 4.4 Special warnings and precautions for use

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

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.

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose 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 Section 5.3). As a precautionary measure, it is preferable to avoid the use of granisetron during pregnancy.

Breastfeeding
It is unknown whether granisetron or its metabolites are excreted in human milk. As a 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

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 (≥1/1000 to <1/100),
Rare (≥1/10 000 to <1/1000),
Very rare (<1/10,000).
<table>
<thead>
<tr>
<th>Immune system disorders</th>
<th>Hypersensitivity reactions e.g. anaphylaxis, urticaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Extrapyramidal reactions</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>QT Prolongation</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Constipation</td>
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<tr>
<td></td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Elevated hepatic transaminases*</td>
</tr>
</tbody>
</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 the 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-HT$_3$ 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 catatotoxic 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-HT$_3$ receptors are located. The released serotonin activates vagal neurons via the 5-HT$_3$ 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-HT$_3$) 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-HT$_3$ 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 4.4).

5.2 **Pharmacokinetic properties**

Pharmacokinetics of the oral administration is linear up to 2.5-fold of the recommended dose in adults. 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 generally not 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 unaltered 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 to patients without hepatic involvement. Despite these changes, no dosage adjustment is necessary (see section 4.2).

**Paediatric population**

These tablets are not recommended in children.

**Elderly 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, 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 repolarization 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 PROPERTIES**

6.1 **List of excipients**

**Tablet Core:**
Cellulose Microcrystalline (E460),
Sodium Starch Glycolate (Type A),
Lactose Monohydrate,
Hypermellose (E464),
Magnesium Stearate (E572).

**Film Coating:**
HPMC 2910/ Hypermellose 6 cP (E464)
Titanium Dioxide (E171)
Macrogol/ PEG 6000
Polysorbate 80 (E433)
For 2 mg: Iron Oxide Yellow (E172)

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**

PVC/PVdC/Aluminium blisters: Pack-size of 5 or 10 film-coated tablets

Not all pack sizes may be marketed.
6.6 Special precautions for disposal and other handling

There are no special requirements.

7 MARKETING AUTHORISATION HOLDER
Dawa Limited
5 Sandridge Close
Harrow
Middlesex
HA1 1XD
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 30684/0193

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
16/05/2011

10 DATE OF REVISION OF THE TEXT
01/03/2013