SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Granisetron 1 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 mg granisetron (as hydrochloride).

Excipient with known effect:

Each tablet contains 55.78 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white tablet embossed "GS" on one side and plain on the reverse

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Granisetron tablets are indicated in adults for the prevention and treatment of acute nausea and vomiting associated with chemotherapy and radiotherapy.

Granisetron 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 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 one hour before the start of therapy.
Dexamethasone has been used concomitantly at doses up to 20 mg once a day orally.

Maximum Dose and Duration of Treatment
Granisetron is also available as ampoules for intravenous administration. The maximum dose of granisetron administered orally and/or intravenously over 24 hours should not exceed 9 mg.

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

Older people and renal impairment
There are no special precautions required for its use in either elderly patients or those patients with renal 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

Granisetron is contraindicated in patients hypersensitive to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

As granisetron may reduce lower bowel motility, patients with signs of sub-acute intestinal obstruction should be monitored 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.dolasetron, ondansetron) has been reported.

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

Serotonin Syndrome

Concomitant administration of granisetron and buprenorphine/opioids may result in serotonin syndrome, a potentially life threatening condition (see section 4.5).

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Granisetron is essentially 'sodium free' as it contains less than 1 mmol sodium (23 mg) per dose (2 mg). To be used with caution in children or in patients on a low sodium diet.

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.

Serotonergic medicinal products (e.g. SSRIs and SNRIs): there have been reports of serotonin syndrome following concomitant use of 5-HT3 antagonists and other serotonergic medicinal products (including SSRIs and SNRIs) (see section 4.4).

Granisetron should be used cautiously when co-administered with:
- Buprenorphine/opioids as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

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.

Breast-feeding
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

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)

Immune system disorders	
Uncommon	Hypersensitivity reactions e.g. anaphylaxis, urticaria
Psychiatric disorders	
Common	Insomnia
Nervous system disorders	
Very common	Headache
Uncommon	Extrapyramidal Reactions
Uncommon	Serotonin Syndrome (see also sections 4.4 and 4.5)
Cardiac disorders	
Uncommon	QT prolongation
Gastrointestinal disorders	
Very common	Constipation
Common	Diarrhoea
Hepatobiliary disorders	
Common	Elevated hepatic transaminases*
Skin and subcutaneous tissue disorders	
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).

As with other 5-HT3 antagonists, cases of serotonin syndrome (including altered mental status, autonomic dysfunction and neuromuscular abnormalities) have been reported following the concomitant use of granisetron and other serotonergic drugs (see sections 4.4 and 4.5).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

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 mgof granisetron as a single injection have been reported, with symptoms of mild headache but no other reported squeals.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (5HT3) antagonists.
ATC code: A04AA02.

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 cytotoxic 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-HT_3) receptors. Radio-ligand binding studies have demonstrated that granisetron has negligible affinity for other receptor types including 5-HT and dopamine D_2 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 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 unchanged granisetron averages 12% of dose whilst that of metabolites amounts to about 47% of dose. The remainder is excreted in faeces as metabolites. Mean plasma half-life in patients is approximately 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.

Older people
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 ofcarcinogenicity 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

Tablet core:
Lactose Monohydrate
Cellulose, Microcrystalline
Hypromellose
Sodium Starch Glycolate (type A)
Magnesium Stearate

Film-coat:
Titanium Dioxide (E171)
Hypromellose
Macrogol 400
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

36 months.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/PVDC aluminium foil opaque blisters in a cardboard carton containing 1,2,4,5,6,7,10,14,20,28,30,50,90,100,150,200,250 and 500 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Generics [UK] Ltd t/a Mylan
Station Close
Potters Bar
Herts
EN6 1TL

8. MARKETING AUTHORISATION NUMBER

PL 04569/0688

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/10/2005

10 DATE OF REVISION OF THE TEXT

01/04/2021