

# Summary of Product Characteristics

## 1. Name of the medicinal product

Setron 1 mg tablets

## 2. Qualitative and quantitative composition

Each tablet contains 1 mg granisetron (as hydrochloride)

Excipients with known effect:

Each tablet contains 55.78 mg of lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take this medicine.

For the full list of excipients, see section 6.1.

## 3. Pharmaceutical form

Tablet.

White to off white round tablets with embossment 'GS' on one side and plain on the other.

## 4. Clinical particulars

### 4.1 Therapeutic indications

Setron 1 mg tablets are indicated for the prevention of nausea and vomiting induced by cytostatic therapy.

### 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 Setron 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 Setron 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 contra-indicated 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-HT<sub>3</sub> antagonists, ECG changes including QT interval prolongation have been reported with granisetron. In patients with preexisting arrhythmias or cardiac conduction disorders this might lead to

clinical consequences. Therefore, caution should be exercised in patients with cardiac comorbidities, on cardiotoxic chemotherapy and/or with concomitant electrolyte abnormalities (see section 4.5.)

Cross-sensitivity between 5-HT<sub>3</sub> antagonists (e.g. dolasteron, ondansetron) has been reported.

#### 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.

#### 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-HT<sub>3</sub> 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 antiulcer 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-HT<sub>3</sub> 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.

#### 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**

### 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-HT<sub>3</sub> antagonists.

Frequency categories are as follows:

Very common: ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare ( $< 1/10,000$ )

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

\*Occurred at a similar frequency in patients receiving comparator therapy

### Description of selected adverse reactions

As for other 5-HT<sub>3</sub> antagonists, ECG changes including QT prolongation have been reported with granisetron (see sections 4.4 and 4.5).

As with other 5-HT<sub>3</sub> 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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il>

Additionally, you can also report to [www.perrigo-pharma.co.il](http://www.perrigo-pharma.co.il).

## **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 (5HT<sub>3</sub>) 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-HT<sub>3</sub> 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 cytotoxic substances, serotonin (5-HT) is released from enterochromaffin cells in the small intestinal mucosa, which are adjacent to the vagal afferent neurons on which 5HT<sub>3</sub> receptors are located. The released serotonin activates vagal neurons via the 5-HT<sub>3</sub> 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 antiemetic and highly selective antagonist of 5-hydroxytryptamine (5-HT<sub>3</sub>) receptors. Radioligand binding studies have demonstrated that granisetron has negligible affinity for other receptor types including 5-HT and dopamine D<sub>2</sub> 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<sub>3</sub> 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 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 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 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**

Microcrystalline cellulose

Lactose monohydrate

Sodium starch

Hypromellose

Magnesium stearate

coating:

Opadry consists of:

Hydroxy propyl methyl cellulose

Titanium dioxide

Macrogol 400

Polysorbate 80

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

The expiry date is indicated on the packaging materials

**6.4 Special precautions for storage**

Store in a cool place, below 25°C

**6.5 Nature and contents of container**

PVC/PVDC blister containing 10 tablets

**Special precautions for disposal and other handling**

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

**7. Manufacturer and Registration holder**

Perrigo Israel Pharmaceuticals LTD

P.O.B 16 Yeruham

**8. Registration number**

108-57-29244-00

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