1.3.1.1 Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ASPEN GRANISETRON 1 mg film-coated tablets

ASPEN GRANISETRON 2 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of ASPEN GRANISETRON 1 mg contains 1,0 mg of granisetron as granisetron hydrochloride.

Contains sugar: Lactose anhydrous 69,38 mg

Each film-coated tablet of ASPEN GRANISETRON 2 mg contains 2,0 mg of granisetron as granisetron hydrochloride.

Contains sugar: Lactose anhydrous 138,76 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

ASPEN GRANISETRON 1 mg: triangular, white, biconvex film-coated tablets, with ‘G1’ engraved on one side OR triangular, white, biconvex film-coated tablets, with “C” debossed on one side and “45” debossed on the other side.

ASPEN GRANISETRON 2 mg: triangular, white, biconvex film-coated tablets, with ‘G2’

engraved on one side OR triangular, white, biconvex film-coated tablets, with “C” debossed on one side and “46” debossed on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ASPEN GRANISETRON is indicated for the prevention of:

- acute and delayed nausea and vomiting associated with chemotherapy (CINV) and radiotherapy (RINV).

4.2. Posology and method of administration

Posology

Adults

Chemotherapy Induced Nausea and Vomiting (CINV)

Prevention:

The dose of ASPEN GRANISETRON is 1 mg twice a day or 2 mg once a day, for up to one week following chemotherapy. The first dose of ASPEN GRANISETRON should be administered within one hour before the start of therapy.

Radiotherapy Induced Nausea and Vomiting (RINV)

The dose of ASPEN GRANISETRON is 2 mg once a day, for up to one week following radiotherapy. The first dose of ASPEN GRANISETRON should be administered within one hour before the start of therapy.

Special populations

Geriatrics:

No dosage adjustments required.

Renal impairment:

No dosage adjustments required.

Hepatic Impairment:

No dosage adjustments required.

Although present experience indicates that no dosage adjustment is required, care should be exercised when administering ASPEN GRANISETRON to elderly patients and patients with renal or hepatic impairment.

Paediatric population

ASPEN GRANISETRON is contraindicated in children under the age of 2 years (see section 4.3).

There is insufficient information to recommend use of ASPEN GRANISETRON in the prevention of RINV in children.

Method of administration

For oral administration.

4.3. Contraindications

ASPEN GRANISETRON is contraindicated in:

- Patients with hypersensitivity to granisetron, other 5-HT_3 antagonists or to any excipients in ASPEN GRANISETRON (see section 6.1).
- Children under the age of 2 years.
- Patients with congenital long QT syndrome.
- Pregnancy and lactation (see section 4.6).

4.4. Special warnings and precautions for use

Lower bowel motility

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

ASPEN GRANISETRON does not stimulate gastric or intestinal peristalsis. It should not be used instead of nasogastric suction. The use of ASPEN GRANISETRON in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distension.

QT interval prolongation

ECG changes including QT interval prolongation has been reported with granisetron, as in ASPEN GRANISETRON. Therefore, ASPEN GRANISETRON should be used with caution in patients with pre-existing dysrhythmias or cardiac conduction disorders, or patients who have, or may develop prolongation of the QT interval, as these may lead to clinical consequences.

Patients with cardiac diseases (such as congestive heart failure or brady-dysrhythmias), patients on cardiotoxic chemotherapy, with concomitant electrolyte abnormalities and/or on concomitant medicines that prolong the QT interval, are particularly at risk and caution should be exercised (see section 4.5).

Hypokalaemia and hypomagnesaemia should be corrected prior to ASPEN GRANISETRON administration.

Cross-sensitivity

Cross-sensitivity between 5-HT_3 antagonists (e.g., dolasteron, ondansetron) has been reported (see section 4.3 and 4.5).

Serotonin syndrome

There have been reports of serotonin syndrome with the use of 5-HT_3 antagonists either alone, but mostly in combination with other serotonergic medicines (including selective

serotonin reuptake inhibitors (SSRIs), and serotonin noradrenaline reuptake inhibitors (SNRIs) (see section 4.5).

Concomitant administration of ASPEN GRANISETRON and buprenorphine/opioids may result in serotonin syndrome, a potentially life-threatening condition.

If concomitant treatment with other serotonergic medicines 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

ASPEN GRANISETRON is contraindicated in children under the age of 2 years (see section 4.3).

There is insufficient clinical evidence to recommend administration of ASPEN GRANISETRON to children.

Excipients

ASPEN GRANISETRON contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients with the rare hereditary problems of galactose intolerance, galactosaemia, total lactase deficiency or glucose-galactose malabsorption or fructose intolerance should not take ASPEN GRANISETRON.

4.5. Interaction with other medicines and other forms of interaction

Other 5-HT_3 antagonists

Cross-sensitivity between 5-HT_3 antagonists (e.g., dolasteron, ondansetron) has been reported (see section 4.3).

Phenobarbitone

The metabolism of granisetron, as in ASPEN GRANISETRON, is induced by the cytochrome P450 inducer phenobarbitone which may cause a 25 % increase in total plasma clearance of ASPEN GRANISETRON.

Ketoconazole

In *in vitro* human microsomal studies, ketoconazole inhibited ring oxidation of granisetron, as in ASPEN GRANISETRON. However, given the absence of pK/pD relationship with granisetron, these changes are believed to have no clinical consequences.

Medicines known to prolong QT interval

Cases of ECG modifications including QT prolongation have been reported with granisetron, as in ASPEN GRANISETRON. In patients concurrently treated with medicines known to prolong QT interval and/or which are dysrhythmogenic, this may lead to clinical consequences (see section 4.4).

Serotonergic medicines (e.g., SSRIs and SNRIs):

There have been reports of serotonin syndrome following concomitant use of 5-HT_3 antagonists and other serotonergic medicines (including SSRIs and SNRIs).

ASPEN 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).

Tramadol

ASPEN GRANISETRON may increase the levels of tramadol.

General

ASPEN GRANISETRON may be co-administered with benzodiazepines (lorazepam), neuroleptics (haloperidol) and anti-ulcer medicines (cimetidine) commonly prescribed with anti-emetic treatments.

Additionally, granisetron, as in ASPEN GRANISETRON, has shown no apparent interaction with emetogenic cancer chemotherapies.

No specific interaction studies have been conducted in anaesthetised patients, but ASPEN GRANISETRON has been safely administered with commonly used anaesthetic and analgesic medicines.

In addition, *in-vitro* human microsomal studies have shown that the cytochrome P450 subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic medicine) is not modified by ASPEN GRANISETRON.

4.6. Fertility, pregnancy and lactation

The use of ASPEN GRANISETRON during pregnancy and lactation is not recommended as safety and efficacy have not been established (see section 4.3).

Pregnancy

There is limited amount of data from the use of ASPEN GRANISETRON in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, avoid the use of ASPEN GRANISETRON during pregnancy.

Breastfeeding

It is unknown whether granisetron or its metabolites are excreted in human milk. As a precautionary measure, breastfeeding should not be advised during use with ASPEN GRANISETRON.

Fertility

In rats, granisetron, as in ASPEN GRANISETRON, had no harmful effects on reproductive performance or fertility.

4.7. Effects on ability to drive and use machines

ASPEN GRANISETRON has no or negligible influence on the ability to drive and use machines.

Since adverse reactions such as headache, dizziness, drowsiness and blurred vision have been reported in patients receiving ASPEN GRANISETRON, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that ASPEN GRANISETRON does not adversely affect their ability to do so (see section 4.8).

4.8. Undesirable effects

a) Summary of the safety profile

The most frequently reported adverse reactions for ASPEN GRANISETRON are headache and constipation, which may be transient. ECG changes including QT prolongation have been reported with granisetron, as in ASPEN GRANISETRON (see section 4.4 and 4.5).

b) Tabulated list of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown (cannot be estimated from the available data)
Infections and infestations			Infections, urinary tract infection
Blood and the lymphatic system disorders			Anaemia, leukocytosis
Immune system disorders		Immediate hypersensitivity reactions including anaphylaxis, urticaria	
Psychiatric disorders	Insomnia	Somnolence, agitation, anxiety	
Nervous system disorders	Headache	Dizziness, drowsiness, seizures and movement disorders, including extrapyramidal reactions such as dystonia, dyskinesia and oculogyric crisis, serotonin syndrome	
Eye disorders			Transient visual disturbances such as blurred vision
Cardiac disorders		Chest pain, tachycardia, bradycardia, dysrhythmias, atrial fibrillation, transient ECG changes including QT interval prolongation	
Vascular disorders		Hypotension, hypertension	
Gastrointestinal disorders	Constipation, hiccups, abdominal pain, diarrhoea, nausea, vomiting	Dyspepsia, taste disturbances	
Hepatobiliary disorders	A transient rise in hepatic transaminases		
Skin and subcutaneous tissue disorders		Rash	
General disorders and administrative site conditions			Asthenia, fever, fatigue

c) Description of selected adverse reactions

Cases of serotonin syndrome (including altered mental status, autonomic dysfunction and neuromuscular abnormalities) have been reported following the concomitant use of granisetron, as in ASPEN GRANISETRON, and other serotonergic medicines (see section 4.4 and 4.5).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088/ +27 (0)11 239-6200

4.9. Overdose

Symptoms

Headaches may occur. Granisetron, as in ASPEN GRANISETRON, may prolong the QT interval.

Treatment

There is no specific antidote for ASPEN GRANISETRON. In the case of overdosage, symptomatic and supportive treatment should be given. ECG monitoring is recommended in case of overdose with ASPEN GRANISETRON.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 5.7.2 Anti-emetics and anti-vertigo preparations

Pharmacotherapeutic group: Antiemetics and antinauseants, serotonin ($5HT_3$) antagonists.

ATC code: A04AA02

Mechanism of action

Granisetron is a selective antagonist of 5-hydroxytryptamine $(5\text{-HT})_3$ receptors with anti-emetic properties. Radioligand binding studies have demonstrated that granisetron has negligible affinity for other receptor types including other 5-HT and dopamine D_2 binding sites.

Serotonin receptors of the 5-HT_3 type are located peripherally in vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. During chemotherapy induced vomiting, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT_3 receptors, which triggers a response from the vagal afferent receptors and the emetic centre is then stimulated, inducing vomiting.

5.2. Pharmacokinetic properties

Absorption

Granisetron is absorbed after oral administration, with peak plasma concentrations occurring 2 hours after dosing. Due to first-pass metabolism, the oral bioavailability of granisetron is about 60 %.

Oral bioavailability is generally not influenced by food.

Distribution

Granisetron is extensively distributed, with a mean volume of distribution of about 3 ℓ/kg.

Plasma protein binding is approximately 65 %.

Biotransformation

Granisetron is metabolised primarily by 7-hydroxylation.

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

Elimination

The pharmacokinetics of granisetron exhibit considerable inter-individual variation.

The elimination half-life is reported to be approximately 3 to 4 hours in healthy individuals and about 9 to 12 hours in cancer patients.

Mean plasma half-life (t½) in patients is approximately 9 hours, with a wide inter-individual variability.

Granisetron clearance is not affected by renal impairment, but is lower in the elderly and in patients with hepatic impairment.

Clearance is predominantly by hepatic metabolism. Urinary excretion of unchanged granisetron averages 12 % of dose while that of metabolites amounts to about 47 % of the dose.

The remainder is excreted in faeces as metabolites.

The pharmacokinetics of granisetron demonstrate no marked deviations from linear pharmacokinetics at oral doses up to 2,5-fold the recommended clinical dose.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

ASPEN GRANISETRON 1 mg

Hypromellose, lactose anhydrous, macrogol, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, sodium starch glycolate, talc, titanium dioxide (C.I. 77891).

ASPEN GRANISETRON 2 mg

Hypromellose, lactose anhydrous, macrogol, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, sodium starch glycolate, talc, titanium dioxide (C.I. 77891).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store at or below 25 °C protected from light and moisture.

Keep in original packaging until required for use.

6.5. Nature and contents of container

1, 5, 10 and 100 film-coated tablets are packed in a white opaque polyvinyl chloride film blister strip sealed with an aluminium foil backing. The blister strips are packed into an outer cardboard carton together with a leaflet.

Not all pack sizes are necessarily marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead

2191

8. REGISTRATION NUMBERS

ASPEN GRANISETRON 1 mg: 42/5.7.2/1007

ASPEN GRANISETRON 2 mg: 42/5.7.2/1008

9. DATE OF FIRST AUTHORISATION

ASPEN GRANISETRON 1 mg: 09 October 2009

ASPEN GRANISETRON 2 mg: 09 October 2009

10. DATE OF REVISION OF TEXT

27 JANUARY 2022

Die Afrikaanse Professionele Inligting is op versoek beskikbaar.

Mediese Blitslyn: 0800 118 088.

ASPEN GRANISETRON 2 mg:

Namibia: NS2 10/5.7.2//0622