PROFESSIONAL INFORMATION FOR GRANICIP

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

GRANICIP 1 mg (tablets)

GRANICIP 2 mg (tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

GRANICIP 1 mg:	Each film-coated tablet contains granisetron hydrochloride equivalent to 1 mg granisetron.

Contains sugar: Lactose monohydrate 37,50 mg

GRANICIP 2 mg:	Each film-coated tablet contains granisetron hydrochloride equivalent to 2 mg granisetron.

Contains sugar: Lactose monohydrate 75 mg

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Film-coated tablets.

GRANICIP 1 mg: White to off-white barrel-shaped film-coated biconvex tablets with ‘G1’ debossed on one side and plain on the other.

GRANICIP 2 mg: White to off-white barrel-shaped film-coated biconvex tablets with ‘G2’

debossed on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Radiotherapy induced nausea and vomiting (RINV) prevention

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

Special populations

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

Paediatric population

GRANICIP is contraindicated in children under the age of 2 years (see **section 4.3).** There is insufficient information to recommend the use of GRANICIP in the prevention of

radiotherapy-induced nausea and vomiting (RINV) in children.

Method of administration

For oral administration.

4.3 Contraindications

- Patients with known hypersensitivity to granisetron, other 5-HT3 antagonists or to any of the excipients used in the formulation of GRANICIP (see **section 6.1**).
- Children under the age of 2 years.
- Pregnancy and lactation (see **section 4.6**).
- Patients with congenital long QT syndrome.

4.4 Special warnings and precautions for use

As GRANICIP may reduce lower bowel motility, patients with signs of subacute intestinal obstruction should be monitored following administration of GRANICIP.

The maximum dose of GRANICIP to be administered over 24 hours should not exceed 9 mg (120 µg/kg).

Cases of myocardial ischemia have been reported in patients treated with ondansetron. In some patients, especially in the case of intravenous administration, symptoms appeared immediately after administration of ondansetron. Patients should be alerted to the signs and symptoms of myocardial ischaemia.

GRANICIP does not stimulate gastric or intestinal peristalsis. It should not be used instead of nasogastric suction. The use of GRANICIP 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 GRANICIP. Therefore, GRANICIP 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 GRANICIP administration.

Cross-sensitivity

Cross-sensitivity between 5-HT3 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-HT3 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 GRANICIP 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.

Lactose monohydrate

GRANICIP contains lactose.

Patients with the rare hereditary problems of galactose intolerance, galactosaemia, total lactase deficiency or glucose-galactose malabsorption or fructose intolerance should not take GRANICIP, which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Other 5-HT3 antagonists

Cross-sensitivity between 5-HT3 antagonists (e.g., dolasteron, ondansetron) has been reported (see **section 4.3**).

Phenobarbitone

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

Ketoconazole

In in vitro human microsomal studies, ketoconazole inhibited ring oxidation of granisetron, as in GRANICIP. 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 GRANICIP. 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-HT3 antagonists and other serotonergic medicines (including SSRIs and SNRIs).
GRANICIP 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

GRANICIP may increase the levels of tramadol.

General

GRANICIP may be co-administered with benzodiazepines, neuroleptics and anti-ulcer medications commonly prescribed with anti-emetic treatments. Additionally, GRANICIP has shown no apparent interaction with emetogenic cancer chemotherapies.
No specific interaction studies have been conducted in anaesthetised patients, but GRANICIP 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 agents) is not modified by GRANICIP.

4.6 Fertility, pregnancy and lactation

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

4.7 Effects on ability to drive and use machines

There have been reports of somnolence with the use of GRANICIP, and this will affect the ability of a patient to drive or operate machinery. Patients should not drive or use machinery or engage in other activities requiring mental alertness and coordination until they have established how GRANICIP affects them.

4.8 Undesirable effects

The following side-effects may occur with use of GRANICIP**:**

Blood and lymphatic system disorders

Less frequent:	Anaemia, leucopenia and thrombocytopenia have been reported.

Nervous system disorders

Frequent:	Headache.
Less frequent:	Fainting, agitation, dizziness, drowsiness and insomnia.

Cardiac disorders

Less frequent:	Dysrhythmias,chest pain, tachycardia, bradycardia, atrial fibrillation and transient ECG changes including QT interval prolongation.
Frequency unknown:	Myocardial ischemia (see **section 4.4**)

Gastrointestinal disorders

Frequent:	Constipation, abdominal pain and diarrhoea.
Less frequent:	Dyspepsia and unusual taste in mouth. Anorexia has also been reported.

Hepatobiliary disorders

Frequent:	A rise in hepatic transaminases may occur.

Skin and subcutaneous tissue disorders

Less frequent:	Alopecia has been reported.

General disorders and administrative site conditions

Frequent:	Unusual tiredness or weakness.
Less frequent:	Cases of allergic reactions, including anaphylaxis have been reported. Other allergic reactions, including minor skin rashes have less frequently been reported and Fever.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8 or to Cipla Medpro (Pty) Ltd by e-mail at

drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

Headache may occur. There is no specific antidote for GRANICIP. In the case of overdosage, symptomatic treatment should be given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 5.7.2 Anti-emetics and anti-vertigo preparations.

Pharmacotherapeutic group: Antiemetics and antinauseants, serotonin (5HT3) antagonists.

ATC code: A04AA02

Pharmacodynamics:

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

Serotonin receptors of the 5-HT3 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-HT3 receptors, which triggers a response from the vagal afferent receptors and the emetic centre is then stimulated, inducing vomiting.

5.2 Pharmacokinetic properties

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 %. Granisetron has an apparent volume of distribution of about 3 L/kg. Plasma protein binding is approximately 65 %. The pharmacokinetics of granisetron exhibit considerable inter-

individual variation. The elimination half-life is reported to be approximately 3 - 4 hours in healthy individuals and about 9 - 12 hours in cancer patients. Granisetron is metabolised primarily by 7-hydroxylation, with less than 20 % of a dose recovered unchanged in urine, and the remainder being excreted in faeces and urine as metabolites.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

GRANICIP 1 mg and GRANICIP 2 mg

Microcrystalline cellulose (Avicel PH 101)

Lactose monohydrate

Sodium starch glycollate (Primojel B)

Maize starch

Magnesium stearate

Film coating for GRANICIP 1 mg and GRANICIP 2 mg

Opadry 04F58804 white:

Hydroxy propyl methyl cellulose

Titanium dioxide (C.I. 77891)

Polyethylene glycol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C in a cool dry place. Protect from light.

Keep the blisters in the outer carton until required for use.

6.5 Nature and contents of container

GRANICIP 1 mg**:** Tablets in PVC film-aluminium foil blister-strips in an outer carton in packs of 5 or 10 tablets.

GRANICIP 2 mg**:** Tablets in PVC film-aluminium foil blister strips in an outer carton in packs of 5 or 10 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9,

Parc du Cap.

Mispel Street,

Bellville,

7530

Customer Care: 080 222 6662

8 REGISTRATION NUMBER(S)

GRANICIP 1 mg: 41/5.7.2/0397

GRANICIP 2 mg: 41/5.7.2/0398

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 June 2009

10 DATE OF REVISION OF THE TEXT

29 May 2023