PROFESSIONAL INFORMATION FOR

NOCIPAL 250 µg/ 5 mL (SOLUTION FOR INJECTION)

SCHEDULING STATUS

S4

1. NAME OF MEDICINE

NOCIPAL (Palonosetron 250 µg/ 5 mL-Solution for injection)

2. QUALITATIVE AND QUANTITAIVE COMPOSITION

Each 5 mL vial contains palonosetron hydrochloride equivalent to palonosetron 250 µg (palonosetron 50 µg/ 1 mL).

Contains sugar: Mannitol (18,50 mg / vial)

Sodium free

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

3. PHARMACEUTICAL FORM

Solution for injection

A clear, colourless solution free from visible particles in a 5 mL glass vial.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

NOCIPAL is indicated for:

the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

4.2. Posology and method of administration

Posology

Adults:

A single, intravenous bolus dose of 250 µg should be administered approximately 30 minutes prior to the start of chemotherapy. NOCIPAL should be injected over 30 seconds. Repeated dosing of NOCIPAL within a seven day interval is not recommended.

The efficacy of NOCIPAL in the prevention of nausea and vomiting induced by highly emetogenic chemotherapy may be augmented by the addition of corticosteroid administered prior to chemotherapy.

Children and adolescents:

NOCIPAL should not be used in patients under the age of 18.

Elderly:

No dosage adjustment is required in the elderly (patients older than 65 years).

Use in patients with renal impairment:

No dosage adjustment is required in patients with impaired renal function.

Data is not available for haemodialysis patients with end stage renal disease.

Patients with hepatic impairment:

No dosage adjustment is required in patients with impaired hepatic function.

Method of administration

For intravenous use only.

4.3. Contraindications

Hypersensitivity to palonosetron or any other ingredient of NOCIPAL listed in **section 6.1**.

4.4. Special warnings and precautions for use

Gastrointestinal effects:

Patients with a history of constipation or signs of sub-acute intestinal obstruction should be monitored as palonosetron as in NOCIPAL may increase large bowel transit time.

Cases of constipation with faecal impaction requiring hospitalisation have been reported in association with palonosetron 750 micrograms.

Cardiac effects:

At the tested dose levels, palonosteron did not induce clinically relevant prolongation of the QTc interval. However, caution should be exercised when prescribing 5-HT_3 receptor antagonists, including palonosetron as in NOCIPAL, with other medicines that prolong the QT interval or in patients who have or are likely to develop increased QT interval. These conditions included patients with a personal or family history of QT prolongation, electrolyte abnormalities, congestive heart failure, bradydysrhythmias, conduction disturbances and in patients taking anti- dysrhythmic medicines or other medical products that lead to QT prolongation or electrolyte abnormalities. Hypokalemia and hypomagnesemia should be corrected prior to 5-HT_3-antagonist administration.

There have been reports of serotonin syndrome with the use of 5-HT_3 antagonists either alone or in combination with other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRI) and

serotonin noradrenaline reuptake inhibitors (SNRIs). Appropriate observation of patients for serotonin syndrome-like symptoms is advised.

NOCIPAL should not be used to prevent or treat nausea and vomiting in the days following chemotherapy if not associated with another chemotherapy administration.

Excipient information

NOCIPAL contains less than 1 mmol sodium (23 mg) per vial, i.e essentially “sodium free”.

4.5. Interaction with other medicines and other forms of interaction

There have been reports of transient ECG changes in some patients taking 5-HT_3 antagonists. As a result, there is a need for caution when NOCIPAL is given together with medicines that prolong the QT interval.

Palonosetron is mainly metabolised by CYP2D6, with minor contribution by CYP3A4 and CYP1A2 isoenzymes. Based on *in vitro* studies, palonosetron does not inhibit or induce cytochrome P450 isoenzymes at clinically relevant concentrations.

Chemotherapeutic medicines:

It has been reported that palonosetron as in NOCIPAL does not inhibit the anti-tumour activity of cisplatin, cyclophosphamide, cytarabine, doxorubicin and mitomycin C.

Inducers and inhibitors of CYP2D6:

Pharmacokinetics studies have shown that palonosetron as in NOCIPAL clearance is not significantly affected by co-administration with CYP2D6 inducers (such as dexamethasone and rifampicin) or inhibitors like amiodarone, celecoxib, chlorpromazine, cimetidine, doxorubicin, fluoxetine, haloperidol, paroxetine, quinidine, ranitidine, ritonavir, sertraline or terbinafine.

Co-administration of the CYP2D6 inhibitor metoclopramide (when administered orally) with a single intravenous dose of palonosetron as in NOCIPAL did not result in any significant pharmacokinetic interactions.

Serotonergic medicines (e.g. SSRIs and SNRIs)

Serotonin syndrome following concomitant use of 5-HT_3 antagonists and other serotonergic medicines (including SSRIs and SNRIs) may occur.

Others:

NOCIPAL has been demonstrated to be safe for use with the following medicines:

- Corticosteroids
- Analgesics
- Other anti-emetics and anti-nauseants
- Antispasmodics
- Anti-cholinergics

4.6. Fertility, pregnancy and lactation

Pregnancy

There is no experience of palonosetron as in NOCIPAL in human pregnancy, therefore, NOCIPAL should not be used in pregnant women.

Breastfeeding

There is no data concerning excretion of palonosetron in breast milk, breast-feeding should be discontinued during therapy.

Fertility

There are no data concerning the effect of palonosetron on fertility.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Palonosetron as in NOCIPAL may cause fatigue, dizziness or somnolence, patients should be cautioned about driving and using machines until they know how NOCIPAL affect them.

4.8. Undesirable effects

Immune system disorders:

Less frequent:	Hypersensitivity, anaphylaxis, anaphylactic / anaphylactoid reactions and shock.

Metabolism and nutrition disorders:

Less frequent:	Hyperkalaemia, metabolic disorders, hypocalcaemia, anorexia, hyperglycaemia, decreased appetite, hypokalaemia.

Psychiatric disorders:

Less frequent:	Anxiety, euphoria.

Nervous system disorders:

Frequent:	Headache, dizziness.
Less frequent:	somnolence, insomnia, paraesthesia, hypersomnia, peripheral sensory neuropathy, seizures.

Eye disorders:

Less frequent:	Eye irritation, amblyopia.

Ear and labyrinth disorders:

Less frequent:	Motion sickness, tinnitus.

Cardiac disorders:

Less frequent: Tachycardia, bradycardia, extrasystoles, myocardial ischaemia, sinus tachycardia, sinus arrhythmia, supraventricular extrasystoles.

Vascular disorders:

Less frequent: Hypotension, hypertension, vein discolouration, vein distended.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Hiccups.

Gastrointestinal disorders:

Frequent: Constipation, diarrhoea.

Less frequent: Dyspepsia, abdominal pain, upper abdominal pain, dry mouth, flatulence.

Hepato-biliary disorders:

Less frequent: Hyperbilirubinaemia.

Skin and subcutaneous tissue disorders:

Less frequent: Allergic dermatitis, pruritic rash.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Arthralgia.

Renal and urinary disorders:

Less frequent: Urinary retention, glycosuria.

General disorders and administration site conditions:

Less frequent: Asthenia, pyrexia, fatigue, feeling hot, influenza-like illness.
Hypersensitivity reactions and injection site reactions (burning induration, discomfort and pain).

Investigations:

Less frequent: Elevated transaminases, hypokalaemia, electrocardiogram QT prolonged.

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 at drugsafetysa@cipla.com.

4.9. Overdose

No known cases of overdose have been reported. Doses of up to 6 mg have been used in clinical trials. In the event of overdose with NOCIPAL, this should be managed with supportive care. Due to the large volume of distribution; dialysis is unlikely to be an effective treatment for NOCIPAL overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

A 5.10 Serotonin antagonists

Pharmacotherapeutic group: Antiemetics and anti-nauseant, serotonin ($5HT_3$) antagonists.

ATC code: A04AAOS

Palonosetron is a potent and selective serotonin subtype 3 ($5\text{-}HT_3$) receptor antagonist. Palonosetron has a high (*in vivo* and *in vitro*) affinity for $5\text{-}HT_3$ and little or no affinity for other bioreceptors, including other serotonergic receptors like $5\text{-}HT_1$, $5\text{-}HT_2$ and $5\text{-}HT_4$. Major human metabolites of palonosetron, namely, M9 and M4, have marginal clinically non-relevant activity.

5.2. Pharmacokinetic properties:

Absorption

After intravenous administration, initial palonosetron plasma levels are decreased, followed by slow elimination with a mean terminal half-life of approximately 40 hours or 2 days. Mean maximum plasma concentration C_{max} and palonosetron exposure ($AUC_{0-\infty}$) are dose-proportional over the range of 0,3 to 90 µg/kg in healthy subjects and in cancer patients.

Distribution

At the recommended dose, palonosetron is widely distributed in the body with a volume of distribution being approximately 6,9 to 7,9 L/kg.

Palonosetron is approximately 62 % bound to plasma proteins.

Metabolism

Approximately 40 % of palonosetron is eliminated renally, while approximately 50 % is metabolised to form the two primary metabolites, M9 and M4, which make up less than 1 % palonosetron $5\text{-}HT_3$ activity. *In vitro* studies have shown that CYP2D6 is the principal isoenzyme responsible for metabolism of palonosetron, while CYP3A4 and CYP1A2 also metabolise palonosetron to a lesser extent. However, there are no clinical differences in the pharmacokinetic parameters between main and poor metabolisers

of CYP2D6 substrates. Palonosetron is not involved in the induction or inhibition of cytochrome P450 isoenzymes at clinically relevant concentrations.

Elimination

Following a single intravenous dose of 10 µg/kg [^{14}C]-palonosetron, about 80 % of the dose was recovered within 144 hours in the urine with palonosetron amounting to approximately 40 % of the administered dose, as the unchanged active substance.

In healthy subjects, the total body clearance of palonosetron was reported to be 173 ±73 mL/min after a single intravenous bolus administration. The low total body clearance and large distribution volume resulted in a terminal half-life in plasma of approximately 40 hours. In 10 % of patients, the mean terminal elimination half-life was greater than 100 hours.

Pharmacokinetics in special populations

Elderly patients:

Age does not have an effect on the pharmacokinetics of palonosetron. No dose adjustments are required in the elderly.

Gender:

Gender does not have an effect on the pharmacokinetics of palonosetron. No gender-based dose adjustments are required.

Paediatric patients:

There is no difference in pharmacokinetic data in patients below 18 years of age and in healthy adults.

Renal insufficiency:

Mild to moderate renal impairment does not have a significant effect on pharmacokinetic parameters.

Severe renal impairment decreases renal clearance with no change in total body clearance. Dose adjustment is not required in patients with renal impairment.

There is no pharmacokinetic data in patients on haemodialysis.

Hepatic insufficiency:

Hepatic impairment does not have a significant effect on total body clearance of palonosetron. Severe hepatic impairment results in an increase in terminal elimination half-life and mean systemic exposure of palonosetron, however dose reduction is not necessary in these patients.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Edetate disodium, sodium citrate, citric acid monohydrate hydrochloric acid, and sodium hydroxide, hydrochloric acid and water for injection.

6.2. Incompatibilities

NOCIPAL must not be mixed with other medicines.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at or below 30 °C. Do not refrigerate.

Any unused solution should be discarded after opening the vial.

6.5. Nature and contents of container

Palonosetron Hydrochloride Injection 0,25 mg/5 mL vial is supplied in a 5 ml USP type I flint glass vial with 20 mm grey chlorobutyl rubber stopper (Ready to use) and 20 mm aluminium blue flip-off seal.

6.6. Special precautions for disposal and other handling

NOCIPAL is for single use only. Any unused solution should be discarded.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD

Parc du Cap

Building 9

Mispel Street

Bellville

7530

RSA

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

50/5.10/0752

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09 December 2022

10. DATE OF REVISION OF THE TEXT

Not applicable