PROFESSIONAL INFORMATION FOR ONICIT

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

ONICIT Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of solution contains 50 micrograms palonosetron (as palonosetron hydrochloride).

Each vial of 5 mL of solution contains 250 micrograms palonosetron (as palonosetron hydrochloride).

ONICIT solution is an isotonic solution for injection.

Contains sugar (mannitol).

Each 1 mL of ONICIT contains 41,5 mg mannitol.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, essentially colourless solution free from evidence of contamination.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ONICIT is indicated for:

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

4.2 Posology and method of administration

Posology

Use in adults

250 micrograms ONICIT administered as a single intravenous bolus approximately 30 minutes before the start of chemotherapy. ONICIT should be injected over 30 seconds.

Repeated dosing of ONICIT within a seven-day interval is not recommended.

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

Special populations

Use in elderly

No dose adjustment is necessary in the elderly.

Use in patients with renal impairment

No dose adjustment is necessary for patients with impaired renal function.

No data is available for patients with end stage renal disease undergoing haemodialysis.

Use in patients with hepatic impairment

No dose adjustment is necessary for patients with impaired hepatic function.

Paediatric population

Use in patients under 18 years of age is not recommended.

Method of administration

For intravenous use.

4.3 Contraindications

- Hypersensitivity to palonosetron or to any of the excipients of ONICIT (listed in section 6.1).
- Congenital long QT syndrome.
- Concomitant use with other medicines that prolong QT interval.
- Uncompensated acute and chronic liver failure.
- Concomitant use with apomorphine is contraindicated (see section 4.4 and section 4.5).

4.4 Special warnings and precautions for use

As ONICIT may increase large bowel transit time, patients with a history of constipation or signs of sub-acute intestinal obstruction should be monitored following administration.

At all dose levels tested (0,25 mg, 0,75 mg and 2,25 mg), ONICIT did not induce clinically relevant prolongation of the QTc interval. However, as for other 5-HT_3 antagonists, caution should be exercised in the concomitant use of ONICIT with medicines that increase the QT interval or in patients who have or are likely to develop prolongation of the QT interval. These conditions include patients with a personal or family history of QT prolongation, electrolyte abnormalities, congestive heart failure, brady-dysrhythmias, conduction disturbances and in patients taking anti-dysrhythmic medicines or other medicines that lead to QT prolongation. Hypokalaemia and hypomagnesaemia should be corrected prior to ONICIT administration.

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

There have been reports of serotonin syndrome with the use of ONICIT either alone or in combination with other serotonergic medicines.

Hypersensitivity reactions may occur in patients who previously exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists.

4.5 Interaction with other medicines and other forms of interaction

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

Apomorphine

Concomitant use of ONICIT and apomorphine may intensify QT prolongation (see section 4.3). Co-administration of ONICIT with apomorphine may cause profound hypotension and loss of consciousness.

Chemotherapeutic medicines

In preclinical studies, ONICIT did not inhibit the anti-tumour activity of the five chemotherapeutic medicines tested (cisplatin, cyclophosphamide, cytarabine, doxorubicin and mitomycin C).

Cardiotoxic medicines

Concomitant use of ONICIT with cardiotoxic medicines e.g. anthracyclines (such as doxorubicin, daunorubicin) or trastuzumab, antibiotics (such as erythromycin), antifungals (such as ketoconazole), anti-dysrhythmics (such as amiodarone) and beta-blockers (such as atenolol or timolol) may cause increased dysrhythmias (see section 4.4).

Metoclopramide

In a clinical study, no significant pharmacokinetic interaction was shown between a single intravenous dose of ONICIT and steady state concentration of oral metoclopramide, which is a CYP2D6 inhibitor.

CYP2D6 inducers and inhibitors

In a population pharmacokinetic analysis, it has been shown that there was no significant effect on ONICIT clearance when co-administered with CYP2D6 inducers (dexamethasone and rifampicin) and inhibitors (including amiodarone, celecoxib, chlorpromazine, cimetidine, doxorubicin, fluoxetine, haloperidol, paroxetine, quinidine, ranitidine, ritonavir, sertraline or terbinafine).

QT prolonging medicines

Caution should be exercised when ONICIT is co-administered with medicines that cause electrolyte abnormalities (see section 4.4).

Corticosteroids

ONICIT has been administered with corticosteroids.

Other medicines

ONICIT has been administered with analgesics, anti-emetic medicines, antispasmodics and anti-cholinergic medicines.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

Since there is no data concerning excretion of ONICIT in breast milk, breastfeeding should be discontinued during therapy.

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.

Since ONICIT may induce dizziness, somnolence or fatigue, patients should be cautioned when driving

or operating machines.

4.8 Undesirable effects

Summary of the safety profile

In clinical studies at a dose of 250 micrograms (total 633 patients) the most frequently observed adverse reactions, at least possibly related to ONICIT, were headache (9 %) and constipation (5 %).

Tabulated summary of adverse reactions

In the clinical studies the following adverse reactions were observed as possibly or probably related to ONICIT and are listed below according to the standard system organ class of MedDRA. These were classified as common (≥ 1/100 to < 1/10) or uncommon (≥ 1/1 000 to < 1/100).

MedDRA System organ class	**Frequency**	**Adverse reaction**
Metabolism and nutrition disorders	Uncommon	Hyperkalaemia, hypokalaemia, metabolic disorders, hypocalcaemia, anorexia, hyperglycaemia, decreased appetite
Psychiatric disorders	Uncommon	Anxiety, euphoric mood
Nervous system disorders	Common	Headache, dizziness
	Uncommon	Somnolence, insomnia, paraesthesia, hypersomnia,

		peripheral sensory neuropathy
Eye disorders	Uncommon	Eye irritation, amblyopia
Ear and labyrinth disorders	Uncommon	Motion sickness, tinnitus
Cardiac disorders	Uncommon	Tachycardia, bradycardia, extrasystoles, myocardial ischaemia, sinus tachycardia, sinus dysrhythmia, supraventricular extrasystoles, QTc prolongation (including *Torsade de Pointes*)
Vascular disorders	Uncommon	Hypotension, hypertension, vein discolouration, vein distended
Respiratory, thoracic and mediastinal disorders	Uncommon	Hiccups
Gastrointestinal disorders	Common	Constipation, diarrhoea
	Uncommon	Dyspepsia, abdominal pain, upper abdominal pain, dry

		mouth, flatulence
Hepato-biliary disorders	Uncommon	Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Uncommon	Allergic dermatitis, pruritic rash
Musculoskeletal and connective tissue disorders	Uncommon	Arthralgia
Renal and urinary disorders	Uncommon	Urinary retention, glycosuria
General disorders and administration site conditions	Uncommon	Asthenia, pyrexia, fatigue, feeling hot, influenza like illness
Investigations	Uncommon	Elevated transaminases

Very rare cases (< 1/10 000) of hypersensitivity reactions (including anaphylaxis, anaphylactic/anaphylactoid reactions and shock) and injection site reactions (burning, induration, discomfort and pain) were reported post-marketing.

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.

4.9 Overdose

No case of overdose has been reported.

Doses of up to 6 mg have been used in clinical trials. The highest dose group showed a similar incidence of adverse events compared to the other dose groups and no dose response effects were observed. In the unlikely event of overdose with ONICIT, this should be managed with supportive care. Dialysis studies have not been performed, however, due to the large volume of distribution, dialysis is unlikely to be an effective treatment for ONICIT overdose.

Palonosetron may cause prolongation of QT interval. ECG monitoring is recommended in cases of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A. 5.10 Serotonin antagonists

Palonosetron is a selective serotonin subtype 3 ($5\text{-}HT_3$) receptor antagonist with a strong binding affinity for this receptor - both *in vitro* and *in vivo*. Palonosetron has little or no affinity for other bioreceptors, including other serotonergic receptors ($5\text{-}HT_1$, $5\text{-}HT_2$ and $5\text{-}HT_4$).

The major human metabolites, M9 and M4, have only marginal clinically non-relevant activity.

5.2 Pharmacokinetic properties

Absorption

Following intravenous administration, an initial decline in plasma concentrations is followed by slow elimination from the body with a mean terminal elimination half-life of approximately 2 days [40 hours]. Mean maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC0-□) are generally dose-proportional over the dose range of 0,3 – 90 µg/kg in healthy subjects and in cancer patients.

Distribution

Palonosetron at the recommended dose is widely distributed in the body with a volume of distribution of approximately 8,3 to 2,5 L/kg.

Approximately 62 % of palonosetron is bound to plasma proteins.

Metabolism

Palonosetron is eliminated by dual route, about 40 % eliminated through the kidney and with approximately 50 % metabolised to form two primary metabolites, M9 and M4, which have less than 1 % of the 5-HT_3 receptor antagonist activity of palonosetron.

In vitro metabolism studies have shown that CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 isoenzymes are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolisers of CYP2D6 substrates. Palonosetron does not inhibit or induce cytochrome P450 isoenzymes at clinically relevant

concentrations.

Elimination

After a single intravenous dose of 10 micrograms/kg [^{14}C]-palonosetron, approximately 80 % of the dose was recovered within 144 hours in the urine, of which approximately 40 % of the administered dose is unchanged active substance.

After a single intravenous bolus administration in healthy subjects the total body clearance of palonosetron was 173 ± 73 mL/min and renal clearance was 53 ± 29 mL/min. The low total body clearance and large volume of distribution resulted in a terminal elimination half-life in plasma of approximately 40 hours. Ten percent of patients have a mean terminal elimination half-life greater than 100 hours.

Pharmacokinetics in special patient groups

Elderly

Age does not affect the pharmacokinetics of palonosetron. No dose adjustment is necessary in elderly patients.

Gender

Gender does not affect the pharmacokinetics of palonosetron. No dose adjustment is necessary based on gender.

Renal impairment

Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters.

Severe renal impairment reduces renal clearance, however, total body clearance in these patients is similar to healthy subjects. No dose adjustment is necessary in patients with renal insufficiency.

No pharmacokinetic data in haemodialysis patients are available.

Hepatic impairment

Hepatic impairment does not significantly affect total body clearance of palonosetron compared to healthy subjects. While the terminal elimination half-life and mean systemic exposure of palonosetron is increased in the subjects with severe hepatic impairment, this does not warrant dose reduction.

Paediatric population

No pharmacokinetic data are available in patients below 18 years of age.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Disodium edetate

Sodium citrate

Citric acid monohydrate

Water for injection

Sodium hydroxide solution

Hydrochloric acid solution

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store at or below 25 °C. Do not refrigerate.

Protect from light. Store vial in carton until required for use.

Upon opening of the vial, any unused solution should be discarded.

6.5 Nature and contents of container

ONICIT is supplied in a Type I glass vial with grey chlorobutyl rubber stopper and blue aluminium cap. It is available in packs of 1 vial containing 5 mL of solution.

6.6 Special precautions for disposal and other handling

Single use only, any unused solution should be discarded.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biomab Innovation (Pty) Ltd

Woodmead Office Park, 3 Stirrup Lane

Van Reenens Avenue

Woodmead, 2144

Biomab Innovation (Pty) Ltd

8. REGISTRATION NUMBER

A40/5.10/0322

9. DATE OF FIRST AUTHORISATION

01 December 2006

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18 September 2023

Manufacturer: OSO Biopharmaceuticals Manufacturing LLC, Albuquerque, NM, USA

NAMIBIA: S2

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