

## **SCHEDULING STATUS:**

S4

## **PROPRIETARY NAME AND DOSAGE FORM**

**ONICIT** (solution for injection)

## **COMPOSITION**

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

Each vial of 5 ml of solution contains 250 micrograms palonosetron (as hydrochloride). **ONICIT** solution is an isotonic solution for injection.

### **Inactive excipients**

Mannitol, disodium edetate, sodium citrate, citric acid monohydrate, water for injection, sodium hydroxide solution and hydrochloric acid solution.

## **PHARMACOLOGICAL CLASSIFICATION**

A. 5.10 Serotonin antagonists

## **PHARMACOLOGICAL ACTION**

### **Pharmacodynamic properties**

#### **Mode of Action**

Palonosetron is a potent and selective serotonin subtype 3 (5-HT<sub>3</sub>) 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-HT<sub>1</sub>, 5-HT<sub>2</sub> and 5-HT<sub>4</sub>).

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

## **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 ( $AUC_{0-\infty}$ ) 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 6.9 to 7.9 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<sub>3</sub> 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 [<sup>14</sup>C]-palonosetron, approximately 80% of the dose was recovered within 144 hours in the urine with palonosetron representing approximately 40% of the administered dose, as unchanged active substance.

After a single intravenous bolus administration in healthy subjects the total body clearance of palonosetron was 173±73ml/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 dosage adjustment is necessary in elderly patients.

#### **Gender:**

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

#### **Paediatric patients:**

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

#### **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 dosage 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.

### **INDICATIONS**

Onicit 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.

### **CONTRA-INDICATIONS**

Hypersensitivity to the active substance, palonosetron.

Hypersensitivity to any excipients listed under 'Composition'.

## **WARNINGS**

As palonosetron may increase large bowel transit time, patients with a history of constipation or signs of sub-acute intestinal obstruction should be monitored following administration. Two cases of constipation with faecal impaction requiring hospitalisation have been reported in association with palonosetron 750 micrograms.

At all dose levels tested, palonosetron did not induce clinically relevant prolongation of the QTc interval.

However, as for other 5-HT<sub>3</sub> antagonists, caution should be exercised in the concomitant use of palonosetron with medicinal products that increase the QT interval or in patients who have or are likely to develop prolongation of the QT interval.

### **Effects on the ability to drive and use machines**

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

Since palonosetron may include dizziness, somnolence or fatigue, patients should be cautioned when driving or operating machines.

## **INTERACTIONS**

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 agents:

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

Metoclopramide:

In a clinical study, no significant pharmacokinetic interaction was shown between a single intravenous dose of palonosetron 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 palonosetron 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).

Corticosteroids:

Palonosetron has been administered safely with corticosteroids.

Other medicinal products:

Palonosetron has been administered safely with analgesics, anti-emetic/anti-nauseants, antispasmodics and anti-cholinergic medicinal products.

## **PREGNANCY AND LACTATION**

There is no experience of palonosetron in human pregnancy, therefore, palonosetron should not be used in pregnant women. Since there is no data concerning excretion of palonosetron in breast milk, breast-feeding should be discontinued during therapy.

## **DOSAGE AND DIRECTIONS FOR USE**

### **For intravenous use**

#### **Use in adults**

250 micrograms palonosetron 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.

#### **Use in children and adolescents**

Use in patients under 18 years of age is not recommended until further data becomes available.

#### **Use in elderly**

No dosage adjustment is necessary in the elderly.

#### **Use in patients with renal impairment**

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

### **Instructions for use and handling**

Single use only, any unused solution should be discarded.

### **SIDE EFFECTS AND SPECIAL PRECAUTIONS**

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%).

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, <1/10) or uncommon (>1/1 000, <1/100).

#### **Metabolism and nutrition disorders**

*Uncommon:* Hyperkalaemia, 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 arrhythmia, supraventricular extrasystoles

### **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:* Dermatitis allergic, 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, hypokalaemia, electrocardiogram QT prolonged

Very rare cases (<1/10 000) of hypersensitivity reactions and injection site reactions (burning, induration, discomfort and pain) were reported from post-marketing experience.

## **KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT**

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.

## **IDENTIFICATION**

Clear, essentially colourless solution free from evidence of contamination.

## **PRESENTATION**

**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.

## **STORAGE INSTRUCTIONS**

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.

Keep out of reach of children.

**REGISTRATION NUMBER**

A40/5.10/0322

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF  
REGISTRATION**

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton

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**DATE OF PUBLICATION OF THE PACKAGE INSERT**

20 April 2012

**NAMIBIA: S2**

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