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_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-HT_1, 5-HT_2 and 5-HT_4).

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 (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 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_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. Palonosteron 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 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_3 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).

Corticosteriods:

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

2196

DATE OF PUBLICATION OF THE PACKAGE INSERT

20 April 2012

NAMIBIA: S2

Reg no.07/5.10/0120