NEW ZEALAND PRODUCT DATA SHEET

1. PRODUCT NAME

Periset (4 mg and 8 mg Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ondansetron as hydrochloride dihydrate 4mg
Ondansetron as hydrochloride dihydrate 8mg

Excipient of known effect
Periset also contains lactose

Lactose

If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Periset 4 mg: Yellow, oval, biconvex, film coated tablets embossed with 'BL' on one face and '4' on the other. Each tablet contains 4 mg of ondansetron as ondansetron hydrochloride dihydrate.

Periset 8 mg: Yellow, oval, biconvex, film coated tablets embossed with 'BL' on one face and '8' on the other. Each tablet contains 8 mg of ondansetron as ondansetron hydrochloride dihydrate.

Do not halve the tablets. Dose equivalence when the tablet is divided has not been established. This product is not able to deliver all approved dose regimens.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Periset tablets are indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. Periset tablets are also indicated for the prevention of post-operative nausea and vomiting.

4.2 Dose and method of administration

Do not halve the tablets. Dose equivalence when the tablet is divided has not been established. This product is not able to deliver all approved dose regimens.

Chemotherapy and radiotherapy induced nausea and vomiting

Adults

The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used.

Emetogenic Chemotherapy and Radiotherapy:-

The recommended oral dose is 8mg 1-2 hours before treatment, followed by 8mg orally 12 hours later.

To protect against delayed or prolonged emesis after the first 24 hours, Periset tablets should be continued for up to 5 days after a course of treatment. The recommended oral dose is 8mg to be taken twice daily.

Highly Emetogenic Chemotherapy:-

Periset can be given by oraladministration.

To protect against delayed or prolonged emesis after the first 24 hours, oral treatment with Ondansetron should be continued for up to 5 days after a course of treatment. The recommended oral dose is 8mg to be taken twice daily

Children and Adolescents (aged 6 months to 17 years)

In children with a body surface area of 0.6 to 1.2 m^2 Ondansetron is administered as a single intravenous dose (not available in this product range) of 5mg/m^2 immediately before chemotherapy, followed by 4mg orally twelve hours later. 4mg orally twice daily can be continued for up to 5 days after a course of treatment.

For children with a body surface area of greater than 1.2 m^2 an initial i.v. dose (not available in this product range) of 8 mg is administered immediately before chemotherapy, followed by 8 mg orally 12 hours later. 8mg orally twice daily can be continued for up to five days after a course of treatment.

Alternatively, in children aged 6 months or older, Ondansetron is administered as a single i.v. dose (not available in this product range) of 0.15 mg/kg (not to exceed 8mg) immediately before chemotherapy. This dose may be repeated every four hours for a total of three doses. 4 mg orally twice daily can be continued for up to five days after a course of treatment. Adult doses must not be exceeded.

Elderly

Periset tablets are well tolerated by patients over 65 years and no alteration of dosage, dosing frequency or route of administration are required.

Post-operative nausea and vomiting

Adults

For prevention of post-operative nausea and vomiting, the recommended oral dose is 16mg given one hour prior to anaesthesia.

Children and Adolescents (aged 1 month to 17 years)

No studies have been conducted on the use of orally administered Ondansetron in the prevention or treatment of post-operative nausea and vomiting;

Elderly

There is limited experience in the use of Periset tablets in the prevention of post-operative nausea and vomiting in the elderly, however Periset tablets is well tolerated in patients over 65 years receiving chemotherapy.

Patients with renal impairment

No alteration of daily dosage or frequency of dosing, or route of administration are required.

Patients with hepatic impairment

Clearance of Periset tablets is significantly reduced and serum half-life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients a total daily dose of 8mg should not be exceeded.

Patients with poor sparteine/debrisoquine metabolism

The elimination half-life of ondansetron is not altered in subjects classified as poor metabolisers of sparteine and debrisoquine. Consequently in such patients repeat dosing will give drug exposure levels no different from those of the general population. No alteration of daily dosage or frequency of dosing are required.

4.3 Contraindications

Contraindications

Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.
Hypersensitivity to any component of the preparation.

4.4 Special warnings and precautions for use

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective $5HT_3$ receptor antagonists.

Rarely, transient ECG changes including QT interval prolongation have been reported in patients receiving ondansetron. In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Ondansetron should be administered with caution to patients who have or may develop prolongation of QTc. These conditions include patients with electrolyte abnormalities, with congenital long QT syndrome, or patients taking other medicinal products that lead to QT prolongation.

As ondansetron is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration.

4.5 Interaction with other medicines and other forms of medicine

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly coadministered with it. Specific studies have shown that there are no pharmacokinetic interactions when ondansetron is administered with alcohol, temazepam, frusemide, tramadol or propofol.

Ondansetron is metabolised by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolising ondansetron, enzyme inhibition or reduced activity of one enzyme (e.g. CYP2D6 genetic deficiency) is normally compensated by other enzymes and should result in little or no significant change in overall ondansetron clearance or dose requirement.

Apomorphine

Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.

Phenytoin, Carbamazepine and Rifampicin

In patients treated with potent inducers of CYP3A4 (i.e. phenytoin, carbamazepine, and rifampicin), the oral clearance of ondansetron was increased and ondansetron blood concentrations were decreased.

Tramadol

Data from small studies indicate that ondansetron may reduce the analgesic effect of tramadol.

4.6 Fertility,pregnancy and lactation

Pregnancy

The safety of ondansetron for use in human pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and peri- and post-natal development. However as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.

Breast feeding

Tests have shown that ondansetron passes into the milk of lactating animals. It is therefore recommended that mothers receiving ondansetron should not breast-feed their babies.

4.7 *Effect on ability to drive and use machinery*

In psychomotor testing ondansetron does not impair performance nor cause sedation.

4.8 Undesirable side effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000) including isolated reports. Very common, common and uncommon events were generally determined from clinical trial data. The incidence in placebo was taken into account. Rare and very rare events were generally determined from post-marketing spontaneous data.

The following frequencies are estimated at the standard recommended doses of ondansetron according to indication and formulation. [10]

Immune system disorders

Rare: Immediate hypersensitivity reactions sometimes severe, including anaphylaxis.

Nervous system disorders

Very common: Headache.

Uncommon: Seizures, movement disorders (including extrapyramidal reactions such as oculogyric crisis, dystonic reactions and dyskinesia have been observed without definitive evidence of persistent clinical sequelae).

Eye disorders

The majority of the blindness cases reported resolved within 20 minutes. Most patients had received chemotherapeutic agents, which included cisplatin. Some cases of transient blindness were reported as cortical in origin.

Cardiac disorders

Uncommon: Arrhythmias, chest pain with or without ST segment depression, bradycardia.

Rare: QTc prolongation (including Torsade de Pointes)

Vascular disorders

Common: Sensation of warmth or flushing.

Uncommon: Hypotension.

Respiratory, thoracic and mediastinal disorders
Uncommon: Hiccups.

Gastrointestinal disorders
Common: Constipation.

Hepatobiliary disorders
Uncommon: Asymptomatic increases in liver function tests#.
#These events were observed commonly in patients receiving chemotherapy with cisplatin.

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. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms

There is limited experience of ondansetron overdose. In the majority of cases symptoms were similar to those already reported in patients receiving recommended doses (see Adverse Effects). There is no specific antidote for ondansetron, therefore in cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

The use of Ipecacuanha to treat overdose with ondansetron is not recommended as patients are unlikely to respond due to the anti-emetic action of Periset tablets itself.

Treatment

There is no specific antidote for ondansetron, therefore in cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

The use of Ipecacuanha to treat overdose with ondansetron is not recommended as patients are unlikely to respond due to the anti-emetic action of Periset tablets itself.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetic and antinauseant, Serotonin (5HT3) antagonist

ATC code: not yet assigned

Ondansetron is a potent, highly selective $5HT_3$ receptor-antagonist. Its precise mode of action in the control of nausea and vomiting is not known. Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via $5HT_3$ receptors. Ondansetron blocks the initiation of this reflex.

Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of $5HT_3$ receptors on neurons located both in the peripheral and central nervous system. The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and

vomiting.

Ondansetron does not alter plasma prolactin concentrations.

5.2 Pharmacokinetics properties:

Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism. Peak plasma concentrations are attained approximately 1.5 hours after dosing. For doses above 8mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher oral doses.

Bioavailability is slightly enhanced by the presence of food but unaffected by antacids. The disposition of ondansetron following oral dosing is with a terminal elimination half life of about 3 hours and steady state volume of distribution of about 140L. Ondansetron is not highly protein bound (70-76%) . Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. Less than 5% of the absorbed dose is excreted unchanged in the urine . The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics . The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing. Studies in healthy elderly volunteers have shown slight, but clinically insignificant, age-related increases in both oral bioavailability and half-life of ondansetron.

Gender differences were shown in the disposition of ondansetron, with females having a greater rate and extent of absorption following an oral dose and reduced systemic clearance and volume of distribution (adjusted for weight).

In a clinical study, 51 paediatric patients aged 1 to 24 months received either 0.1 or 0.2 mg/kg ondansetron prior to undergoing surgery. Patients aged 1 to 4 months had a clearance when normalised to body weight that was approximately 30% slower than in patients aged 5 to 24 months but comparable to the patients aged 3 to 12 years. The half-life in the 1 to 4 month patient population was reported to average 6.7 hours compared to 2.9 hours for patients in the 5 to 24 month and 3 to 12 year age range. The differences in pharmacokinetic parameters can be explained in part by the higher volume of distribution in the 1 to 4 month patient population.

In a study of 21 paediatric patients aged between 3 and 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron following a single intravenous dose (not available in this product range) of 2mg (3-7 years old) or 4mg (8-12 years old) were reduced in comparison to values with adult patients. Both parameters increased in a linear fashion with weight and by 12 years of age, the values were approaching those of young adults. When clearance and volume of distribution values were normalised by body weight, the values for these parameters were similar between the different age group populations. . Use of weight-based dosing (0.1mg/kg up to 4mg maximum) compensates for these changes and is effective in normalising systemic exposure in paediatric patients.

In patients with moderate renal impairment (creatinine clearance 15-60mL/min), both systemic clearance and volume of distribution are reduced, resulting in a slight, but

clinically insignificant, increase in elimination half-life (5.4h). A study in patients with severe renal impairment who required regular haemodialysis (studied between dialyses) showed the pharmacokinetics of ondansetron to be essentially unchanged. In patients with severe hepatic impairment, systemic clearance of ondansetron is markedly reduced with prolonged elimination half-lives (15-32h) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism.

5.3 Preclinical Safety Data

No additional data of relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Periset contains the following excipients*Excipients:*

Lactose anhydrous, microcrystalline cellulose, pregelatinised maize starch, and magnesium stearate.

The tablet coating contains the following excipients: hypromellose 5 cps; titanium dioxide; ferric oxide yellow.

Gluten free. Contains Lactose.

6.2 Incompatabilities

Not applicable

6.3 Shelf life

3 years when stored below 25°C.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container. .

Blister packs of 10, 20, 30 and 50 tablets.

Not all pack sizes are available

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

IPCA Pharma (NZ) Pty Limited.
3-A, St. Oswalds Road
Greenland
AUCKLAND 1061

Contact No: + 64 2136 0880

9. DATE OF FIRST APPROVAL

5th October 2006

10 DATE OF REVISION OF THE TEXT

24th February 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
Complete datasheet	Formatting changes