1 ONDANSETRON-CLARIS 2 mg/mL solution for injection

Ondansetron-Claris Solution for Injection 2 mg/mL

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ondansetron-Claris, Solution for Injection, is a clear colourless solution containing the equivalent of 2 mg/mL of Ondansetron. The pH of the solution is 3.30 – 4.00. It is available in 2 mL and 4 mL presentations.

3 PHARMACEUTICAL FORM

Solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ondansetron-Claris is indicated for:

- the prevention and treatment of nausea and vomiting induced by cytotoxic therapy and radiotherapy
- the prevention and treatment of post-operative nausea and vomiting

4.2 Dose and method of administration

The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The dose of Ondansetron-Claris should be flexible in the range of 8-32 mg a day and selected as indicated below. The lowest effective dose should be used.

In order to reduce microbiological contamination hazards, the diluted solutions should be prepared immediately prior to use and infusion commenced as soon as practicable after preparation of the mixture. The diluted infusion solution should be stored under refrigeration (2-8 ºC) and used within 24 hours. The product is for single use in one patient only. Any residue should be discarded.

Administration recommendations: slow intravenous injection (1 mg/hour) from an infusion bag or syringe pump. The following medicines may be administered via the Y-site of the ondansetron giving set for ondansetron concentrations of 16 to 160 micrograms/mL (i.e. 8 mg/500 mL and 8 mg/50 mL respectively).

Cisplatin:
Concentrations up to 0.48 mg/mL (i.e. 240 mg in 500 mL) administered over 1 - 8 hours.

5-fluorouracil:
Concentrations up to 0.8 mg/mL (i.e. 2.4 g in 3 litres or 400 mg in 500 mL) administered at a rate of at least 20 mL per hour (500 mL per 24 hours). Higher concentrations of fluorouracil may cause precipitation of ondansetron. The fluorouracil infusion may contain up to 0.045% w/v magnesium chloride in addition to other excipients shown to be compatible.

Carboplatin:
Concentrations in the range 0.18 mg/mL to 9.9 mg/mL (i.e. 90 mg in 500 mL to 990 mg in 100 mL), administered over ten minutes to one hour.

Etoposide:
Concentrations in the range 0.14 mg/mL to 0.25 mg/mL (i.e. 72 mg in 500 mL to 250 mg in 1 litre), administered over thirty minutes to one hour.

Ceftazidime:
Doses in the range 250 mg to 2000 mg reconstituted with Water for Injections BP as recommended by the manufacturer (i.e. 2.5 mL for 250 mg and 10 mL for 2 g ceftazidime) and given as an intravenous bolus injection over approximately five minutes.
Cyclophosphamide:
Doses in the range 100 mg to 1 g, reconstituted with Water for Injections BP, 5mL per 100 mg cyclophosphamide, as recommended by the manufacturer, and given as an intravenous bolus injection over approximately five minutes.

Doxorubicin:
Doses in the range 10-100 mg reconstituted with Water for Injections BP, 5 mL per 10 mg doxorubicin, as recommended by the manufacturer and given as an intravenous bolus injection over approximately five minutes.

Adults:
Emetogenic chemotherapy and radiotherapy
For the control of chemotherapy or radiotherapy induced emesis or nausea in adults, a single dose of 8mg of ondansetron should be administered as a slow intravenous IV) injection in not less than 30 seconds, or intramuscular injection (IM), immediately before treatment.
Oral treatment is recommended to protect against delayed or prolonged emesis after the first 24 hours.

Highly emetogenic chemotherapy
For patients receiving highly emetogenic chemotherapy, eg. high-dose cisplatin, ondansetron may be administered as a single 8mg intravenous or intramuscular dose by slow intravenous injection in not less than 30 seconds, or intramuscular injection, immediately before chemotherapy. Doses of greater than 8mg and up to a maximum of 16mg of ondansetron may only be given by intravenous infusion diluted in 50-100mL of saline or other compatible infusion fluid and infused over not less than 15 minutes. A single dose of greater than 16 mg should not be given (see 4.4 Special warnings and precautions for use).

Alternatively a dose of 8mg of ondansetron may be administered by slow intravenous injection in not less than 30 seconds or intramuscular injection immediately before chemotherapy, followed by two further intravenous or intramuscular doses of 8mg two to four hours apart, or by a constant infusion of 1mg/hour for up to 24 hours.

The selection of dose regimen should be determined by the severity of the emetogenic challenge.

The efficacy of ondansetron in highly emetogenic chemotherapy may be enhanced by the addition of a single intravenous dose of dexamethasone sodium phosphate, 20mg administered prior to chemotherapy.

Oral treatment is recommended to protect against delayed or prolonged emesis after the first 24 hours.

Post-operative Nausea and Vomiting
For prevention of post-operative nausea and vomiting in adults, ondansetron may be administered as a single dose of 4 mg, given by IM or slow IV injection at induction of anaesthesia.

For treatment of established post-operative nausea and vomiting, a single dose of 4 mg given by IM or slow IV injection is recommended in most patients.

Children and Adolescents:
Emetogenic chemotherapy and radiotherapy (Age 6 months to 17 years)
In children with a body surface area of 0.6-1.2 m2 Ondansetron-Claris may be administered as a single IV dose of 5 mg/m2 immediately before chemotherapy, followed by an oral dose of 4 mg twelve hours later. It may be necessary to provide ongoing medication using an appropriate oral dose form (4 mg twice daily) for up to 5 days after a course of treatment.

For children with a body surface area >1.2 m2 an initial IV dose of 8 mg is administered immediately before chemotherapy, followed by an oral dose of 8 mg twelve hours later. It may be necessary to
provide ongoing medication using an appropriate oral dose form (8 mg twice daily) for up to 5 days after a course of treatment.

Alternatively, in children aged 6 months or more, Ondasetron-Claris may be administered as a single IV dose of 0.15 mg/kg (maximum dose 8 mg) immediately prior to chemotherapy. This dose may be repeated every 4 hours for a total of 3 doses. It may be necessary to provide ongoing medication using an appropriate oral dose form (4 mg twice daily) for up to 5 days after a course of treatment. Adult doses must not be exceeded.

**Post-operative Nausea and Vomiting (Age 1 month to 17 years)**

For prevention of post-operative nausea and vomiting in children having surgery under general anaesthesia, ondansetron may be administered by slow IV injection at a dose of 0.1 mg/kg up to a maximum of 4 mg either prior to, at or after induction of anaesthesia, or after surgery.

**Elderly Patients:**

**Emetogenic chemotherapy and radiotherapy**

Efficacy and tolerance in patients aged over 65 years was similar to that seen in younger adults indicating no need to alter dosage or route of administration in the elderly.

**Post-operative Nausea and Vomiting**

There is limited experience in the use of ondansetron in the prevention and treatment of postoperative nausea and vomiting in the elderly.

**Impaired Renal Function:**

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

**Impaired Hepatic Function:**

Clearance of ondansetron is significantly reduced and the serum half-life significantly prolonged in subjects with moderate or severe impairment of hepatic function. It is recommended that a total daily dose of 8mg should not be exceeded for patients with moderate or severe hepatic dysfunction.

**Patients with Poor Sparteine/Debrisoquine Metabolism**

There is no significant differences in the elimination half-life of ondansetron in patients classified as poor metabolisers of sparteine and debrisoquine. Repeat dosing will result in exposure levels similar to those of the general population. Dosage adjustments are not required.

4.3 **Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 **Special warnings and precautions for use**

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HT3 receptor antagonists.

Ondansetron prolongs the QT interval in a dose-dependent manner. In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Avoid ondansetron in patients with congenital long QT syndrome. Ondansetron should be administered with caution to patients who have or may develop prolongation of QTc, including patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias or patients taking other medicinal products that lead to QT prolongation or electrolyte abnormalities.

Hypokalemia and hypomagnesemia should be corrected prior to ondansetron administration.
As ondansetron increases 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 interaction

Caution should be exercised when ondansetron is co-administered with drugs that prolong the QT interval and/or cause electrolyte abnormalities.

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly co-administered with it. Studies have shown 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.

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

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

Ondansetron-Claris should only be admixed with the infusion solutions recommended below. It is stable for 36 hours in these infusion solutions when kept under refrigeration (2-8°C).

- Sodium chloride I.V. Infusion BP 0.9% w/v
- Glucose I.V. Infusion BP 5% w/v
- Mannitol I.V. Infusion BP 10% w/v
- Ringer’s I.V. Infusion
- Potassium chloride 0.3% w/v and Sodium chloride 0.9% w/v I.V. Infusion BP
- Potassium chloride 0.3% w/v and Glucose 5% w/v I.V. Infusion BP

Compatibility studies have been undertaken in polyvinyl chloride infusion bags and polyvinyl chloride administration sets. It is considered that adequate stability would also be conferred by the use of polyethylene infusion bags or type 1 glass bottles. Dilutions of ondansetron in sodium chloride 0.9% w/v or in glucose 5% w/v have been demonstrated to be stable in polypropylene syringes. It is considered that ondansetron injection diluted with other compatible infusion fluids would be stable in polypropylene syringes.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B1

The safety of ondansetron for use in human pregnancy has not been established therefore its use during pregnancy is not recommended.

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 or peri-natal and post-natal development. However animal studies are not always predictive of human response.

Breast-feeding

Tests have shown that ondansetron is excreted in the breast milk of rats. It is therefore recommended that mothers receiving ondansetron should not breast-feed their babies.

Fertility

No data available.
4.7 Effects on ability to drive and use machines
Ondansetron-Claris is unlikely to have any effect on a person’s ability to drive or operate machinery.

4.8 Undesirable effects
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/].

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.

**Immune system disorders**
Rare: Immediate hypersensitivity reactions, sometimes severe, including anaphylaxis.

**Nervous system disorders**
Very common: Headache.
Uncommon: Extrapyramidal reactions (such as oculogyric crisis/dystonic reactions) and
dyskinesia have been observed without definitive evidence of persistent clinical
sequelae, seizures.
Rare: Dizziness during rapid I.V. administration.

**Eye disorders**
Rare: Transient visual disturbances (e.g. blurred vision) predominantly during I.V.
administration.
Very rare: Transient blindness predominantly during I.V. administration.
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.
**NEW ZEALAND DATA SHEET**

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

**General disorders and administration site conditions**
Common: Local I.V. injection site reactions.

4.9 Overdose
Ondansetron prolongs the QT interval in a dose-dependent fashion. ECG monitoring recommended in cases of overdose.

Little is at known about overdosage with ondansetron, however, a limited number of patients have received overdoses. Symptoms were similar to those reported in patients receiving the recommended doses (see 4.8 Undesirable effects). In all instances, the events resolved completely. There is no specific antidote for ondansetron. In cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Ondansetron is a potent, highly selective 5HT3 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 5HT3 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 due to antagonism of 5HT3 receptors on neurones 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. In psychomotor testing, ondansetron does not impair performance nor cause sedation. Ondansetron does not alter plasma prolactin concentrations.

5.2 Pharmacokinetic properties
The disposition of ondansetron following oral, I.M. or I.V. dosing is similar with a terminal elimination half-life of about 3 hours and steady state volume of distribution of about 140 L.

Equivalent systemic exposure is achieved after intramuscular and intravenous administration of ondansetron. 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 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. No dose adjustment is necessary for patients aged 1 to 4 months as only a single i.v. dose of ondansetron is recommended for the treatment of postoperative nausea and vomiting. 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 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.

Population pharmacokinetic analysis was performed on 74 patients aged 6 to 48 months following administration of 0.15 mg/kg i.v. ondansetron every 4 hours for three doses for the treatment of chemotherapy induced nausea and vomiting and 41 surgery patients aged 1 to 24 months following administration of a single 0.1 mg/kg or 0.2 mg/kg i.v. dose of ondansetron. Based on the population pharmacokinetic parameters for subjects aged 1 month to 48 months, administration of a 0.15 mg/kg i.v. dose of ondansetron every 4 hours for 3 doses would result in a systemic exposure (AUC) comparable to that observed in paediatric surgery subjects aged 5 to 24 months and previous paediatric studies in cancer (aged 4 to 18 years) and surgical (aged 3 to 12 years) subjects, at similar doses.

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 ondansetron's pharmacokinetics to be essentially unchanged. In patients with severe hepatic impairment, ondansetron's systemic clearance 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 data available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Citric acid monohydrate, sodium citrate, sodium chloride and water for injections.

6.2 Incompatibilities
Ondansetron-Claris should not be administered in the same syringe or infusion as any other medication.

Ondansetron-Claris should only be admixed with those infusion solutions which are recommended.

6.3 Shelf life
36 months from date of manufacture.
6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of container
Each ampoule of Ondansetron-Claris Injection 4 mg/2 mL contains ondansetron hydrochloride equivalent to ondansetron 4 mg. Packs of 1 and 5 ampoules.
Each ampoule of Ondansetron-Claris Injection 8 mg/4 mL contains Ondansetron hydrochloride equivalent to Ondansetron 8 mg. Packs of 1 and 5 ampoules.

6.6 Special precautions for disposal
No special requirements.

7 MEDICINE SCHEDULE
Prescription

8 SPONSOR
Ondansetron-Claris is distributed in New Zealand by:
Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland 1060
Phone: (09) 574 2400

9 DATE OF FIRST APPROVAL
03/09/2009

10 DATE OF REVISION OF THE TEXT
13/03/2018

SUMMARY TABLE OF CHANGES
Change to Sponsor details.