
DATA SHEET

ONDANACCORD INJECTION

NAME OF MEDICINE

Ondanaccord (Ondansetron hydrochloride dihydrate) injection 4mg and 8mg

QUALITATIVE AND QUANTITATIVE COMPOSITION

Ondanaccord injection is a clear, colourless, sterile solution. Each 1 mL of aqueous solution contains 2mg ondansetron as the hydrochloride dihydrate. Ondanaccord injection is available in glass ampoules containing ondansetron 4mg in 2mL or ondansetron 8mg in 4mL.

PHARMACEUTICAL FORM

Solution for IM or IV administration.

CLINICAL PARTICULARS

Therapeutic Indications

Ondansetron injection is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. Ondansetron injection is also indicated for the prevention and treatment of post-operative nausea and vomiting.

Posology and method of administration

Ondanaccord is also available for oral use to allow the route of administration and dosing to be flexible.

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.

The dose range of Ondanaccord injection is 8 to 32 mg a day and selected as shown below:-

Emetogenic Chemotherapy and Radiotherapy:-

The recommended intravenous or intramuscular dose of Ondanaccord is 8mg administered as a slow injection 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 Ondanaccord may be administered as a single 8mg intravenous or intramuscular dose immediately before chemotherapy. Doses of greater than 8mg and up to 32mg of Ondanaccord may only be given by intravenous infusion diluted in 50-100mL of saline or other compatible infusion fluid (see Pharmaceutical Precautions) and infused over not less than 15 minutes.

Alternatively a dose of 8mg of Ondanaccord may be administered by slow intravenous 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 Ondanaccord 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.

Children and Adolescents (aged 6 months to 17 years)

In children with a body surface area of 0.6 to 1.2 m² Ondanaccord may be administered as a single intravenous dose of 5mg/m² immediately before chemotherapy, followed by a 4mg oral dose 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 m² an initial i.v. dose 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, Ondanaccord is administered as a single i.v. dose 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

Ondanaccord is 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 dose of Ondanaccord injection is a single dose of 4mg by intramuscular or slow intravenous injection administered at the induction of anaesthesia.

For treatment of established post-operative nausea and vomiting a single dose of 4mg given by intramuscular or slow intravenous injection is recommended.

Children and Adolescents (aged 1 month to 17 years)

For prevention and treatment of PONV in paediatric patients having surgery performed under general anaesthesia, ondansetron may be administered by slow intravenous injection at a dose of 0.1mg/kg up to a maximum of 4mg either prior to, at or after induction of anaesthesia, or after surgery.

Elderly

There is limited experience in the use of Ondanaccord in the prevention and treatment of post-operative nausea and vomiting in the elderly, however Ondanaccord 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 Ondanaccord 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.

Contra-indications

Hypersensitivity to any component of the preparation.

Special warnings and special precautions for use

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

Very rarely and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been reported.

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

Interaction with other medicinal products and other forms of interaction

There is no evidence that ondansetron either induces or inhibits the metabolism of other medicines 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.

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.

Pregnancy and Lactation

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.

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.

Effects on ability to drive and use machines

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

Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10,000$ and $< 1/1000$) and very rare ($\geq 1/10,000$) 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: Seizures, movement disorders (including extrapyramidal reactions such as oculogyric crisis, dystonic reactions and dyskinesia have been observed without definitive evidence of persistent clinical sequelae).

Rare: Dizziness during rapid i.v. administration.

Eye disorders

Rare: Transient visual disturbances (eg. blurred vision) predominantly during i.v. administration.

Very rare: transient blindness predominantly during intravenous 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.

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.

General disorders and administration site conditions

Common: Local i.v. injection site reactions.

Overdose

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 Undesirable 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 Ondanaccord itself.

PHARMACOLOGICAL PROPERTIES

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 probably due to antagonism of 5HT₃ 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.

Pharmacokinetic properties

The disposition of ondansetron following oral, intramuscular or intravenous dosing is similar with a terminal elimination half life of about 3 hours and steady state volume of distribution of about 140L.

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.

Preclinical Safety Data

A study in cloned human cardiac ion channels has shown ondansetron has the potential to affect cardiac repolarisation *via* blockade of HERG potassium channels. The clinical relevance of this finding is uncertain.

PHARMACEUTICAL PARTICULARS

List of excipients

Sodium chloride
citric acid monohydrate
Sodium citrate
Water for injections
Sodium hydroxide (for pH adjustment)
Hydrochloric acid, concentrated (for pH adjustment)

Incompatibilities

Ondansetron injection should not be administered in the same syringe or infusion as any other medication (see Instructions for use/handling).

Ondansetron injection should only be admixed with those infusion solutions which are recommended (see Instructions for use/handling).

Shelf life

Ondanaccord ampoules have a shelf life of 2years.

Special precautions for storage

Protect from light. Store below 25°C.

Nature and Contents of Container

As registered locally.

Instructions for use/handling

Ondanaccord injection ampoules:-

The ampoule formulation is unpreserved and should only be used on a single occasion, injected or diluted immediately after opening; any remaining solution should be discarded.

Ondanaccord injection ampoules should not be autoclaved.

Compatibility with intravenous fluids:-

In keeping with good pharmaceutical practice intravenous solutions should be prepared at the time of infusion. However, unpreserved ondansetron injection has been shown to be

stable for seven days at room temperature (below 25°C) under fluorescent lighting or in a refrigerator with the following intravenous infusion fluids:

Sodium Chloride Intravenous Infusion BP 0.9% w/v.

Glucose Intravenous Infusion BP 5% w/v.

Mannitol Intravenous Infusion BP 10% w/v.

Ringers Intravenous Infusion.

Potassium Chloride 0.3% w/v and Sodium Chloride 0.9% w/v Intravenous Infusion BP.

Potassium Chloride 0.3% w/v and Glucose 5% w/v Intravenous Infusion BP.

Compatibility studies have been undertaken in polyvinyl chloride infusion bags, Polyethylene infusion bags, Glass bottles and Polypropylene syringes. It is considered that adequate stability would also be conferred by the use of polyethylene infusion bags or Type 1 glass bottles.

Dilutions of unpreserved ondansetron injection 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 unpreserved ondansetron injection diluted with compatible infusion fluids recommended above would be stable in polypropylene syringes.

Note: Preparation must be under the appropriate aseptic conditions if extended storage periods are required.

Compatibility with other drugs:-

Ondansetron may be administered by intravenous infusion at 1mg/hour, eg. from an infusion bag or syringe pump. The following drugs may be administered via the Y-site of the ondansetron giving set for ondansetron concentrations of 16 to 160mcg/mL (eg 8mg/500mL and 8mg/50mL respectively);

- Cisplatin: - Concentrations up to 0.48mg/mL (eg. 240mg in 500mL) administered over one to eight hours.
- 5-fluorouracil: - Concentrations up to 0.8mg/mL (eg 2.4g in 3 litres or 400mg in 500mL) administered at a rate of at least 20mL per hour (500mL per 24 hours). Higher concentrations of 5-fluorouracil may cause precipitation of ondansetron. The 5-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 0.18mg/mL to 9.9mg/mL (eg 90mg in 500mL to 990mg in 100mL), administered over ten minutes to one hour.
- Etoposide: - Concentrations in the range 0.144mg/mL to 0.25mg/mL (eg. 72mg in 500mL to 250mg in 1 liter), administered over thirty minutes to one hour.
- Ceftazidime: - Doses in the range 250mg to 2000mg reconstituted with Water for Injections BP as recommended by the manufacturer (eg. 2.5mL for 250mg and

10mL for 2g ceftazidime) and given as an intravenous bolus injection over approximately five minutes.

- Cyclophosphamide:- Doses in the range 100mg to 1g, reconstituted with Water for Injections BP, 5mL per 100mg cyclophosphamide, as recommended by the manufacturer, and given as an intravenous bolus injection over approximately five minutes.
- Doxorubicin:- Doses in the range 10-100mg reconstituted with Water for Injections BP, 5mL per 10mg doxorubicin, as recommended by the manufacturer and given as an intravenous bolus injection over approximately five minutes.

MEDICINES CLASSIFICATION

Prescription Only Medicine

NAME AND ADDRESS

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