New Zealand Datasheet

Name of Medicine
ONDANACCORD Injection
Ondansetron hydrochloride dihydrate injection 4 mg and 8 mg.

Presentation
ONDANACCORD Injection is a sterile solution that is clear and colourless. Each 1 mL of aqueous solution contains 2 mg of ondansetron (as hydrochloride dihydrate).

ONDANACCORD injection is available in a 2 mL clear or amber glass ampoule containing 4 mg ondansetron (as hydrochloride dihydrate).

ONDANACCORD injection is also available a 4 mL clear or amber glass ampoule containing 8 mg ondansetron (as hydrochloride dihydrate).

Indications
ONDANACCORD injection is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.

ONDANACCORD injection is also indicated for the prevention and treatment of post-operative nausea and vomiting.

Dosage and Administration

Chemotherapy- and Radiotherapy-induced Nausea and Vomiting:
Adults
The relative dosages and combinations of cancer treatments influence their potential ability to induce emesis. ONDANACCORD injection can be administered at a dosage of between 8 to 32 mg per day, as described below.

Emetogenic Chemotherapy and Radiotherapy:
For patients receiving emetogenic chemotherapy or radiotherapy, ONDANACCORD injection 8 mg can be administered as a slow intravenous injection in not less than 30 seconds, or intramuscular injection immediately before cytotoxic treatment.

Prophylactic oral treatment is also recommended for delayed or prolonged emesis after the first 24 hours of chemotherapy or radiotherapy administration.

Highly Emetogenic Chemotherapy:
For patients receiving highly emetogenic chemotherapy (for example, high-dose cisplatin), ONDANACCORD injection can be administered using the following dosing schedules, as determined by the severity of the emetogenic challenge:
• ONDANACCORD injection 8 mg as a single intravenous injection in not less than 30 seconds, or intramuscular injection immediately before chemotherapy.

• ONDANACCORD injection at dosages ranging from 8 mg and up to a maximum of 16 mg should be diluted in 50–100 mL saline or another compatible infusion fluid (see “Further Information” and “Pharmaceutical Precautions”) and given as an intravenous infusion over 15 minutes or more immediately before chemotherapy. A single dose of greater than 16 mg should not be given.

• ONDANACCORD injection 8 mg as a slow intravenous injection in not less than 30 seconds or intramuscular injection immediately before chemotherapy followed by two intravenous or intramuscular injections of 8 mg, two or four hours apart (not less than 4 hours apart with repeat intravenous doses), or by a constant intravenous infusion of 1 mg/hour for 24 hours.

In patients receiving highly emetogenic therapy, a single intravenous injection of dexamethasone sodium phosphate 20 mg administered prior to chemotherapy may enhance the efficacy of ONDANACCORD injection.

Prophylactic oral treatment is also recommended for delayed or prolonged emesis after the first 24 hours of chemotherapy or radiotherapy administration.

Children and Adolescents (Aged 6 Months to 17 Years):
In paediatric patients, ONDANACCORD injection dosage can be calculated according to body surface area.

• In children and adolescents with a body surface area of 0.6–1.2m², ONDANACCORD injection 5 mg/m² should be administered as a single intravenous dose immediately prior to chemotherapy followed 12 hours later by a single oral dose of 4 mg. Oral administration at a dosage of 4 mg twice daily can be continued for up to five days following chemotherapy.

• In children and adolescents with a body surface area exceeding 1.2m², ONDANACCORD injection 8 mg should be administered as a single intravenous dose immediately prior to chemotherapy followed 12 hours later by a single oral dose of 8 mg. Oral administration at a dosage of 8 mg twice daily can be continued for up to five days following chemotherapy.

In children aged 6 months or older, ONDANACCORD injection dosage may also be calculated according to bodyweight. ONDANACCORD injection 0.15 mg/kg should be administered as a single intravenous dose immediately before chemotherapy. The intravenous dose must not exceed 8 mg. This dose may be repeated every four hours for a total of three doses. Oral administration at a dosage of 4 mg twice daily can be continued for up to five days following chemotherapy. Dosages must not exceed those recommended in adults.

Elderly Patients:
In patients 65 years of age or older, all intravenous doses should be diluted and infused over 15 minutes and, if repeated, given no less than 4 hours apart.

In patients 65 to 74 years of age, the initial intravenous dose of ondanestron 8 mg or 16 mg, infused over 15 minutes, may be followed by 2 doses of 8 mg infused over 15 minutes and given no less than 4 hours apart.
In patients 75 years of age or older, the initial intravenous dose of ondansetron should not exceed 8 mg infused over 15 minutes. The initial dose of 8 mg may be followed by 2 doses of 8 mg, infused over 15 minutes and given no less than 4 hours apart.

Post-operative Nausea and Vomiting

*Adults*

Prevention of post-operative nausea and vomiting: ONDANACCORD injection 4 mg can be administered as a single slow intravenous or intramuscular injection at the induction of anaesthesia.

Treatment of established post-operative nausea and vomiting: ONDANACCORD injection 4 mg can be administered as a single slow intravenous or intramuscular injection.

*Children and Adolescents (aged 1 Month to 17 Years):*

Prevention or treatment of post-operative nausea or vomiting in paediatric patients having surgery performed under general anaesthesia: ONDANACCORD injection 0.1 mg/kg may be administered as a slow intravenous injection prior to, at or after induction of anaesthesia, or after surgery. The intravenous dose must not exceed 4 mg.

*Elderly Patients:*

There is limited experience with ondansetron for the prevention or treatment of post-operative nausea or vomiting in patients aged 65 years or more; however, ondansetron is well tolerated in elderly patients receiving cytotoxic chemotherapy.

*Patients with Renal Impairment:*

The daily dosage, frequency of dosing or route of administration of ONDANACCORD injection does not require alteration in patients with renal impairment.

*Patients with Hepatic Impairment:*

A total daily dose of ONDANACCORD injection 8 mg should not be exceeded in patients with moderately or severely impaired hepatic function, as the clearance of ondansetron is significantly reduced and the serum half-life is significantly prolonged in these patients.

*Patients with Poor Sparteine/Debrisoquine Metabolism:*

There is no alteration in the elimination half-life of ondansetron in patients with poor sparteine/debrisoquine metabolism; therefore, the daily dosage or frequency of dosing of ONDANACCORD injection does not require modification in such patients as they are not exposed to ondansetron levels different to that of the general population.

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 ONDANACCORD injection preparation.
**Warnings and Precautions**

Patients with hypersensitivity reactions to other selective 5HT₃ receptor antagonists have also reported reactions to ondansetron.

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.

Serotonin syndrome has been described following the concomitant use of ondanestron and other serotonergic drugs (see Interactions). If concomitant treatment with ondanestron and other serotonergic drugs is clinically warranted, appropriate observation of the patient is advised.

Ondansetron increases large bowel transit time; therefore, patients with subacute intestinal obstruction should be monitored following administration of ONDANACCORD injection.

**Use in Pregnancy**

There have been no suggestions in animal studies that ondansetron harms the development of the embryo or foetus or affects the course of gestation and peri- or post-natal development. However, the safety of ondansetron in human pregnancy has not been established and the use of ondansetron in pregnancy is not recommended.

**Use in Lactation**

In experimental animal studies, ondansetron is excreted in breast milk. Breast feeding should be avoided in women receiving ondansetron.

**Effects on Ability to Drive and Use Machines**

Ondansetron has not been shown to impair performance or cause sedation in psychomotor testing.

**Adverse Effects**

Adverse events are tabulated below by system organ class and frequency category, with frequencies estimated at the standard recommended doses of ondansetron according to indication and formulation. Frequencies are categorised 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.

Clinical data was generally used to determine the incidence of very common, common and uncommon events (taking the incidence with placebo into account). Post-marketing
spontaneous reports were generally used to determine the incidence of rare and very rare events.

**Frequency of adverse events with ondansetron.**

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Frequency category</th>
<th>Adverse reaction</th>
<th>Additional notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Rare</td>
<td>Immediate hypersensitivity reaction</td>
<td>Sometimes severe, includes anaphylaxis</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very common</td>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Movement disorders</td>
<td>Including extrapyramidal reactions such as oculogyric crisis, dystonic reactions and dyskinesias(^1)</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Dizziness</td>
<td>During rapid intravenous infusion</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Rare</td>
<td>Transient visual disturbances (e.g. blurred vision)</td>
<td>Predominantly during intravenous administration</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Transient blindness(^2)</td>
<td>Predominantly during intravenous administration</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon</td>
<td>Arrhythmias</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chest pain</td>
<td>With or without ST segment depression</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>QTc prolongation (including Torsade de Pointes)</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Common</td>
<td>Sensation of warmth or flushing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Uncommon</td>
<td>Hiccups</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Constipation</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Uncommon</td>
<td>Asymptomatic increase in liver function tests(^3)</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Very rare</td>
<td>Toxic skin eruption</td>
<td>Including toxic epidermal necrolysis</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common</td>
<td>Local intravenous injection site reactions</td>
<td></td>
</tr>
</tbody>
</table>

1. These have been observed without definitive evidence of persistent clinical sequelae.
2. Most reported cases of transient blindness have resolved within 20 minutes. The majority of affected patients had received chemotherapeutic drug regimens with cisplatin. Some cases of transient blindness were reported as cortical in origin.
3. Commonly in patients receiving chemotherapeutic drug regimens with cisplatin.
Interactions

Pharmacokinetic Interactions
No pharmacokinetic interactions have been reported between ondansetron and alcohol, temazepam, frusemide, tramadol or propofol. Furthermore, no evidence suggests that ondansetron induces or inhibits the metabolism of other drugs frequently co-administered with it.

Caution should be exercised when ondansetron is co-administered with medicines that prolong the QT interval and/or cause electrolyte abnormalities (see Warnings and Precautions).

Ondansetron undergoes hepatic metabolism by several cytochrome P450 enzymes (CYP3A4, CYP2D6 and CYP1A2). Because a number of enzyme pathways are involved in ondansetron metabolism, inhibition or reduced activity of one enzyme is normally compensated for by other pathways and is not expected to have a clinically significant impact on ondansetron clearance or dosage 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
When phenytoin, carbamazepine and rifampicin (potent inducers of CYP3A4) were co-administered with ondansetron, an increase was observed in oral clearance of ondansetron together with a decrease in blood concentrations.

Serotonergic Drugs
Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been described following the concomitant use of ondansetron and other serotonergic drugs, including selective serotonin reuptake inhibitors and serotonin noradrenaline reuptake inhibitors.

Tramadol
Small studies suggest that the analgesic effect of tramadol may be reduced by ondansetron.

Overdosage
Experience with ondansetron overdose is limited. In most cases, symptoms of overdose were similar to adverse effects reported in patients receiving recommended dosages (see Adverse Effects). In patients with suspected overdose, appropriate symptomatic and supportive therapy should be administered. Ondansetron prolongs the QT interval in a dose-dependent fashion and ECG monitoring is recommended in cases of overdose. There is no specific antidote for ondansetron. Ipecacuanha should not be used, as the anti-emetic effects of ondansetron itself are likely to prevent vomiting from being induced.

Pharmaceutical Precautions
Store ONDANACCORD injection below 25 °C and protect from light.
Instructions for Use/Handling
ONDANACCORD injection formulation is unpreserved; therefore, solution within a single ampoule should only be used on one occasion. Immediately after the ampoule is open, the solution should be injected or diluted and any remaining solution should be discarded.

Compatibility with Intravenous Fluids
Unpreserved ondansetron injection has been shown to be stable for seven days at room temperature (below 25°C) or in a refrigerator (2-8 °C) when diluted with the following intravenous infusion fluids:

- Sodium Chloride Intravenous Infusion 0.9 % w/v.
- Glucose Intravenous Infusion 5 % w/v.
- Mannitol Intravenous Infusion 10 % w/v.
- Ringer’s Intravenous Infusion.
- Potassium Chloride 0.3 % w/v and Sodium Chloride 0.9 % w/v Intravenous Infusion.
- Potassium Chloride 0.3 % w/v and Glucose 5 % w/v Intravenous Infusion.

Compatibility studies have been undertaken in polyvinyl chloride infusion bags with polyvinyl chloride administration sets, polyethylene infusion bags, Type 1 glass bottles and polypropylene syringes.

Dilutions of Ondansetron Injection in 10 % mannitol injection, ringer’s injection, 0.3 % potassium chloride and 0.9 % sodium chloride injection, 0.3 % potassium chloride and 5 % glucose injection, 0.9 % sodium chloride injection and 5 % glucose injection have been demonstrated to be stable in polyvinyl chloride infusion bags and polyvinyl chloride administration sets, polyethylene infusion bags, Type 1 glass bottles and polypropylene syringes.

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

Compatibility with Other Drugs
ONDANACCORD injection may be administered by intravenous infusion from an infusion bag or syringe pump at a rate of 1 mg/h. Chemotherapeutic drugs may be co-administered via the Y-site of the ONDANACCORD injection giving set at concentrations that allow ondansetron to be delivered at concentrations ranging from 16–160 mcg/mL (8 mg/500 mL to 8 mg/50 mL).

Drugs that may be co-administered with ONDANACCORD injection via the giving set.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration</th>
<th>Length/rate of injection/infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Up to 0.48 mg/mL (e.g. 240 mg in 500 mL)</td>
<td>Infusion over 1–8 hours</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>0.18–9.9 mg/mL (e.g. 90 mg in 500 mL to 990 mg in 100 mL)</td>
<td>Infusion over 10–60 min</td>
</tr>
<tr>
<td>Etoposide</td>
<td>0.14 – 0.25 mg/mL (e.g. 72 mg in 500 mL to 250 mg in 1000 mL)</td>
<td>Infusion over 30–60 min</td>
</tr>
</tbody>
</table>
Ceftazidime          250–2000 mg reconstituted with Water for Injections BP (e.g. 2.5 mL solution for 250 mg ceftazidime; 10 mL solution for 2000 mg ceftazidime) | Intravenous bolus injection over 5 min

Cyclophosphamide     100–1000 mg reconstituted with Water for Injections BP (5 mL solution per 100 mg cyclophosphamide) | Intravenous bolus injection over 5 min

Doxorubicin          10–100 mg reconstituted with Water for Injections BP (5 mL solution per 10 mg doxorubicin) | Intravenous bolus injection over 5 min

1. As recommended by the manufacturer.

**Dexamethasone:**
Dexamethasone sodium phosphate 20 mg may be administered as a slow intravenous injection over 2-5 minutes via the Y-site of an infusion set delivering 8 or 16 mg of ondansetron diluted in 50-100 mL of a compatible infusion fluid over approximately 15 minutes. Compatibility between dexamethasone sodium phosphate and ondansetron has been demonstrated supporting administration of these drugs through the same giving set resulting in concentrations in line of 32 microgram - 2.5 mg/mL for dexamethasone sodium phosphate and 8 microgram – 0.75 mg/mL for ondansetron.

**Incompatibilities**
ONDANACCORD injection should not be administered in the same syringe or infusion as any other medication (see Instructions for Use/Handling).

ONDANACCORD injection should only be mixed with recommended infusion solutions (see Instructions for Use/Handling).

**Package Quantities**
ONDANACCORD injection is available in a 2 mL clear or amber glass ampoule containing 4 mg ondansetron (as hydrochloride dihydrate) or in a 4 mL clear or amber glass ampoule containing 8 mg ondansetron (as hydrochloride dihydrate).

**Medicines Classification**
Prescription medicine.

**Further Information**

**Mechanism of Action**
The emetic effects of cytotoxic chemotherapy and radiotherapy may be a consequence of their ability to induce serotonin 5HT₃ release from cells in the small intestine, which then acts on 5HT₃ receptors in vagal afferent nerves to stimulate a vomiting reflex. In addition, activation of the vagal afferents may further stimulate nausea and vomiting through a central mechanism by causing release of 5HT₃ in the area postrema. Common pathways may exist in the induction of post-operative nausea and vomiting.
Ondansetron Injection 2 mg/mL, 2 mL and 4 mL

Ondansetron is a potent and highly selective antagonist of the 5HT₃ receptor that blocks the vomiting reflex. While its precise mode of action in the control of nausea and vomiting is not known, the effects of ondansetron are attributed to antagonism of 5HT₃ receptors in the peripheral and central nervous system.

Plasma prolactin concentrations are not altered by ondansetron.

**Pharmacokinetics**

Ondansetron has a similar disposition irrespective of whether it is administered orally, intramuscularly or intravenously, with a terminal half-life of approximately 3 hours and a volume of distribution at steady state of approximately 140 litres.

Systemic exposure after intramuscular or intravenous administration of ondansetron is equivalent. Between 70–76% of ondansetron is protein bound. Ondansetron undergoes hepatic metabolism via several enzymatic pathways, with less than 5% of the absorbed dose excreted unchanged in the urine. Ondansetron’s pharmacokinetic profile is unchanged in patients without enzyme CYP2D6 (the debrisoquine polymorphism) and also by repeat dosing. Ondansetron has shown slight increases in oral bioavailability and half-life in healthy elderly subjects; however, these changes were not considered to be clinically significant.

Oral ondansetron has a greater rate and extent of absorption with reduced systemic clearance and volume of distribution in females than males (adjusted for bodyweight).

Pharmacokinetic analyses were performed in infants aged 1–24 months (n=51) who received ondansetron 0.1 or 0.2 mg/kg prior to surgery. Bodyweight-normalised clearance was approximately 30% slower in infants aged 1–4 months than those aged 5–24 months but comparable to patients aged 3–12 years. In infants aged 1–4 months, the ondansetron half-life was an average of 6.7 hours compared with 2.9 hours in individuals aged 5–24 months or 3–12 years. A higher volume or distribution in neonates and infants explains in part the differences in pharmacokinetic parameters in the 1- to 4-month old patient population. As only one single intravenous dose of ondansetron is recommended for the treatment of postoperative nausea and vomiting, no dose adjustment is necessary for infants aged 1–4 months.

A study was performed in children aged 3–12 years undergoing elective surgery with general anaesthesia (n=21) who received a single IV dose of ondansetron 2 mg (those aged 3–7 years) or 4mg (those aged 8–12 years). The absolute values for ondansetron clearance and volume of distribution were reduced compared with those reported in adults. A linear relationship was observed between both parameters and bodyweight, with values approaching those of young adults in study participants aged 12 years.

Bodyweight-normalised clearance and volume of distribution values were similar across age groups. Weight-based dosing (0.1 mg/kg to a maximum of 4mg) compensates for age-related changes and normalises systemic exposure in paediatric patients.

In another study, 74 infants aged 6–48 months with chemotherapy-induced nausea and vomiting received intravenous ondansetron 0.15 mg/kg every four hours (three doses) and 41 infants aged 1–24 months being treated for post-surgical nausea and vomiting received a
single intravenous dose of ondansetron 0.1 or 0.2 mg/kg. Population pharmacokinetic analysis showed that administration of intravenous ondansetron 0.15 mg/kg every four hours (three doses) in infants aged 1–48 months would result in a systemic exposure (AUC) comparable to that observed in infants aged 5–24 months undergoing surgery and that observed in previous studies in cancer patients aged 4–18 years and surgical patients aged 3–12 years at similar doses.

The systemic clearance and volume of distribution of ondansetron are reduced in patients with moderate renal impairment (creatinine clearance 15–60 mL/min); this produces a clinically insignificant increase in elimination half-life (5.4 hours). The pharmacokinetic profile of ondansetron was essentially unaltered in patients with severe renal impairment requiring haemodialysis who were studied between dialyses. The systemic clearance of ondansetron is markedly reduced with a prolonged elimination half-life (15–32 hours) and oral bioavailability approaching 100% in patients with severe hepatic impairment.

**Excipients**

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

**Preclinical Safety data**

An *in-vitro* study in cloned human cardiac ion channels suggests that ondansetron may block hERG potassium channels, possibly affecting cardiac repolarisation. It is unclear if this finding is clinically relevant.

**Name and Address**

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**Date of Preparation**

5 April 2017