Package Insert

ONRON 4 & 8

Ondansetron Injection 2 mg/ mL, 2 mL ampoule & 4 mL ampoule

i. Name and Strength of Active Substance(s):

ONRON 4 & 8: Each ml contains: Ondansetron Hydrochloride Dihydrate Ph. Eur. equivalent to Ondansetron 2 mg

ii. Product Description:

ONRON 4 & 8: A clear colorless solution filled in clear/amber glass ampoule. When examined under suitable conditions of visibility it should be practically free from foreign particles.

List of excipients:

Sodium Chloride,
Sodium citrate,
Citric Acid Monohydrate,
Sodium hydroxide (for pH adjustment),
Hydrochloric Acid Concentrate (for pH adjustment),
Water for Injection.

iii. Pharmacodynamics/Pharmacokinetics:

Pharmacodynamic Properties:

ATC code: - A04 Antiemetics and antinauseants
ATC group: - A04AA01 Serotonin (5HT3) 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.

No significant changes were seen in the measured electrocardiographic PR or QRS intervals.

Pharmacokinetics Properties:

The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

A direct correlation of plasma concentration and anti-emetic effect has not been established.

Absorption

Equivalent systemic exposure is achieved after IM and IV administration of ondansetron.

Distribution
The disposition of ondansetron following oral, intramuscular (IM) and intravenous (IV) dosing is similar steady state volume of distribution of about 140 L.

Ondansetron is not highly protein bound (70-76%).

Metabolism
Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics

Excretion
Less than 5% of the absorbed dose is excreted unchanged in the urine. Terminal half-life is about 3 hours.

Special Patient Populations

Children and Adolescents (aged 2 years and over).

When clearance and volume of distribution values are normalised by body weight, the values for these parameters are similar between the different age group populations. Use of weight-based dosing compensates for age-related changes and is effective in normalising systemic exposure in paediatric patients.

Elderly persons

Early Phase I studies in healthy elderly volunteers showed a slight age-related decrease in clearance, and an increase in half-life of ondansetron. However, wide inter-subject variability resulted in considerable overlap in pharmacokinetic parameters between young (< 65 years of age) and elderly subjects (≥ 65 years of age) and there were no overall differences in safety or efficacy observed between young and elderly cancer patients enrolled in CINV clinical trials to support a different dosing recommendation for the elderly.

Based on more recent ondansetron plasma concentrations and exposure-response modelling, a greater effect on QTcF is predicted in patients ≥ 75 years of age compared to young adults. Specific dosing information is provided for patients over 65 years of age and over 75 years of age for intravenous dosing (*see Dosage and Administration – CINV and RINV in Elderly*)

Renal Impairment
In patients with moderate renal impairment (creatinine clearance 15-60 ml/min), both systemic clearance and volume of distribution are reduced following intravenous administration of ondansetron, resulting in a slight, but clinically insignificant, increase in elimination half-life (5.4h).

Hepatic Impairment
Following oral, intravenous or intramuscular dosing in patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced with prolonged elimination half-lives (15-32 h) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism.

Gender differences
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).

iv. Indication:

Adults:
Management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, Prevention and treatment of post-operative nausea and vomiting (PONV).

Paediatric Population:
Management of chemotherapy-induced nausea and vomiting.
Prevention and treatment of post-operative nausea and vomiting.

v. Recommended Dosage:

For intravenous injection or intramuscular injection or intravenous infusion after dilution.

For instructions on dilution of the product before administration, see section xiii - storage condition.

Prescribers intending to use ondansetron in the prevention of delayed nausea and vomiting associated with chemotherapy in adults, adolescents or children or radiotherapy in adults, should take into consideration current practice and appropriate guidelines.

Chemotherapy and radiotherapy induced nausea and vomiting (CINV and RINV):
Adults: The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The selection of dose regimen should be determined by the severity of the emetogenic challenge.

CINV and RINV in Adults
The recommended intravenous (IV) or intramuscular (IM) dose of *ONRON* is 8 mg administered immediately before treatment.

For highly emetogenic chemotherapy, a maximum initial ondansetron dose of 16 mg IV infused over 15 minutes may be used. A single IV dose greater than 16 mg should not be given due to dose-dependent increase of QT prolongation risk (*see Warnings and Precautions, Adverse Reactions, Pharmacodynamic Effects*).

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

IV doses greater than 8 mg and up to a maximum of 16 mg must be diluted in 50 mL to 100 mL of 0.9% Sodium Chloride Injection or 5% Dextrose Injection before administration and infused over not less than 15 minutes (*see Instructions for Use and Handling*). *ONRON* doses of 8 mg or less, do not need to be diluted and may be administered as a slow IM or IV injection in not less than 30 seconds.

The initial dose of *ONRON* may be followed by 2 additional IV or IM doses of 8 mg 2 to 4 hours apart, or by a constant infusion of 1 mg/h for up to 24 hours.

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

• CINV in Children and Adolescents (aged 2 years and over)

In children with a body surface area of 0.6 to 1.2 m^2 ondansetron is administered as a single IV dose of 5 mg/m^2 immediately before chemotherapy, followed by 4 mg orally 12 hours later. 4 mg orally twice daily can be continued for up to five days after a course of treatment.

• CINV and RINV in Elderly
In patients 65 to 74 years of age, the initial IV dose of *ONRON* 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. All IV doses should be diluted in 50-100 mL of saline or other compatible infusion fluid and infused over 15 minutes

In patients 75 years of age or older, the initial IV dose of *ONRON* 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 (*see Special Patient Populations, Elderly*). All IV doses should be diluted in 50-100 mL of saline or other compatible infusion fluid and infused over 15 minutes.

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

• **Hepatic Impairment**

Clearance of ondansetron 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 8 mg IV or oral 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 is required.

POST-OPERATIVE NAUSEA AND VOMITING
• **PONV in Adults**

For prevention of post-operative nausea and vomiting, the recommended dose of *ONRON* injection is a single dose of 4 mg by IM or slow IV injection administered at the 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.

• **PONV in Children and Adolescents (aged 2 years and over)**

For prevention and treatment of PONV in paediatric patients having surgery performed under general anaesthesia, *ONRON* may be administered by slow IV injection (not less than 30 seconds) 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.

There is limited data on the use of *ONRON* in the prevention and treatment of PONV in children under 2 years of age.

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

• **Renal Impairment**

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

• **Hepatic Impairment**

Clearance of ondansetron 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 8 mg IV or oral 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 is required.

vi. Route of Administration:

For intravenous or intramuscular.

vii. Contraindication:

Hypersensitivity to ondansetron or to any of the excipients listed section ii (*See section* ii).

Hypersensitivity to other selective 5HT3 receptor antagonists (e.g. granisetron, dolasetron).

The concomitant use of apomorphine with ondansetron is contraindicated based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron.

viii. Special Warnings and Precautions for use:

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

Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitive reactions.

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. These include patients with electrolyte abnormalities, with congenital long QT syndrome, congestive heart failure, bradyarrhythmias or patients taking other medicinal products that lead to QT prolongation. Therefore, caution should be exercised in patients with cardiac rhythm or conduction disturbances, in patients treated with anti-arrhythmic agents or beta-adrenergic blocking agents and in patients with significant electrolyte disturbances.

Hypokalemia and hypomagnesemia should be corrected prior to ondansetron administration.

There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs)). If concomitant treatment with ondansetron and other serotonergic drugs is clinically warranted, appropriate observation of the patient is advised.

As ondansetron is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration In patients with adenotonsillar surgery prevention of nausea and vomiting with ondansetron may mask occult bleeding.

Therefore, such patients should be followed carefully after ondansetron.

This medicinal product contains 2.5 mmol (or 57.9 mg) sodium per maximum daily dose of 32 mg. To be taken into consideration by patients on a controlled sodium diet.

Paediatric Population:
Paediatric population receiving ondansetron with hepatotoxic chemotherapeutical agents should be monitored closely for impaired hepatic function.

Chemotherapy-induced nausea and vomiting:
When calculating the dose on a mg/Kg basis and administering three doses at 4 hourly intervals, the total daily dose will be higher than if one single dose of 5 mg/m2 followed by an oral dose is given. The comparative efficacy of these two different dosing regimens has not been investigated in clinical trials. Cross trial comparing indicate similar efficacy for both regimens.

ix. Interactions with Other Medicines and Other Forms of Interaction:

Effects of ondansetron on other medicinal products
There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly co-administered with it. Specific studies have shown that there are no pharmacokinetic interactions when ondansetron is administered with alcohol, temazepan, furosemide, tramadol, morphine, lidocaine, propofol, alfentanil or thiopental.

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

Effects of other medicinal products on ondansetron
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.

Apomorphine: Based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron, the concomitant use of apomorphine with ondansetron is contradindicated.

Use of Ondansetron with QT prolonging drugs may result in additional QT prolongation. Concomitant use of Ondansetron with cardiotoxic drugs (e.g. anthracyclines such as doxorubicin, daunorubicin or trastuzimab), antibiotics (such as erythromycin or ketoconazole), antiarrhythmics (such as amiodarone) and beta blockers (such as atenolol or timolol) may increase the risk of arrhythmias.

There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic drugs (including SSRIs and SNRIs).

x. Use during Pregnancy/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 fetus, the course of gestation and pre- and post-natal development. However as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.

Lactation:

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:

Ondansetron 2mg/ml has no or negligible influence on the ability to drive and use machines.

xi. Undesirable Effects /Adverse Reactions:

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) not known (cannot be estimated from the available 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. Anaphylaxis may be fatal.
Cross-sensitivity has also been observed in patients who are hypersensitive to other selective 5HT3 antagonists.

Nervous system disorders
Very common: Headache.
Uncommon: Seizures, movement disorders (including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia), 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 intravenous 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. Chest pain and cardiac arrhythmias may be fatal in individual cases.

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.

Ondansetron is known to increase the large bowel transit time and may cause constipation in some patients.

Hepatobiliary disorders
Uncommon: Asymptomatic increases in liver function tests.

These events were most frequently observed in patients receiving chemotherapy with cisplatin.

Skin and subcutaneous tissue disorders
Very rare: Toxic skin eruption, including toxic epidermal necrolysis.

General disorders and administration site conditions
Common: local intravenous site reactions.

xii. Overdose and Treatment:

Symptoms and Signs
Little is known at present about over dosage with ondansetron; however, a limited number of patients received overdoses. In the majority of cases, symptoms were similar to those already reported in patients receiving recommended doses. Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second degree AV block.

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

Treatment
In all instances, the events resolved completely. There is no specific antidote for ondansetron, therefore in all 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 ondansetron itself.

xiii. Storage Conditions:

Store below 30°C.
Keep out of the sight and reach of children.
Keep ampoules in the outer carton in order to protect from light.
For storage conditions of the diluted medicinal product, see below.

Special precautions for disposal and other handling
The solution must not be sterilised in an autoclave.

Ondansetron Injection should only be admixed with those infusion solutions which are recommended:

- 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.

The stability of Ondansetron Injection after dilution with the recommended infusion fluids have been demonstrated in concentrations 0.016 mg/ml and 0.64 mg/ml.

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% dextrose 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.

Compatibility with other drugs: Ondansetron Injection may be administered by intravenous infusion using 0.9% sodium chloride and 5% dextrose injection at 1mg/hour, e.g. from an infusion bag or syringe pump. The following drugs may be administered via the Y-site of the Ondansetron Injection giving set for ondansetron concentrations of 16 to 160 micrograms/ml (e.g. 8 mg/500 ml and 8 mg/50 ml respectively);

Cisplatin: Concentrations up to 0.48 mg/ml (e.g. 240 mg in 500 ml) administered over one to eight hours.

Carboplatin: Concentrations in the range 0.18 mg/ml to 9.9 mg/ml (e.g. 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 (e.g. 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 (e.g. 2.5 ml for 250 mg and 10 ml for 2g ceftazidime) and given as an intravenous bolus injection over approximately five minutes.
Cyclophosphamide: Doses in the range 100 mg to 1g, reconstituted with Water for Injections BP, 5 ml 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 10-100mg 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 5 minutes.

Dexamethasone: Dexamethasone sodium phosphate 20mg may be administered as a slow intravenous injection over 2-5 minutes via the Y-site of an infusion set delivering 8 or 16mg 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.

The solution is to be visually inspected prior to use (also after dilution). Only clear solutions practically free from particles should be used.

The diluted solutions should be stored protected from light.

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

Shelf life
Unopened: 3 years.

Injection
After first opening the medicinal product should be used immediately.

Infusion
Chemical and physical in-use stability has been demonstrated for 7 days at 25 °C and 2 °C - 8 °C with the solutions given as in above.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

xiv. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section xiii.

xv. Dosage Forms or Presentation:

ONRON 4 & 8 Solution for Injection or Infusion: Carton containing 5 ampoules.

xvi. Name and Address of Product Registrant:

ACCORD HEALTHCARE PRIVATE LIMITED.
6 Shenton Way # 38-01 OUE Downtown Singapore 068809

xvii. Date of Revision of Package Insert:

21st June 2018