VOMISIQ

Route of Administration	Dosage Form / Strength
Intravenous	Injection/ 2 mg/mL ondansetron (as hydrochloride dihydrate)

INDICATIONS AND CLINICAL USE

Adults

Ondansetron Injection BP (ondansetron hydrochloride) is indicated for:

- The prevention of nausea and vomiting associated with emetogenic chemotherapy, including high dose cisplatin.
- The prevention and treatment of post-operative nausea and vomiting.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Ondansetron hydrochloride is a selective antagonist of the serotonin receptor subtype, 5-HT3. Its precise mode of action in the control of chemotherapy induced nausea and vomiting is not known.

Cytotoxic chemotherapy and radiotherapy are associated with the release of serotonin (5-HT) from enterochromaffin cells of the small intestine, presumably initiating a vomiting reflex through stimulation of 5-HT3 receptors located on vagal afferents. Ondansetron may block the initiation of this reflex. Activation of vagal afferents may also cause a central release of serotonin from the chemoreceptor trigger zone of the area postrema, located on the floor of the Page 15 of 30 fourth ventricle. Thus, the antiemetic effect of ondansetron is probably due to the selective antagonism of 5-HT3 receptors on neurons located in either the peripheral or central nervous systems, or both.

The mechanisms of ondansetron's antiemetic action in post-operative nausea and vomiting are not known.

Pharmacodynamics

In vitro metabolism studies have shown that ondansetron is a substrate for human hepatic cytochrome P450 enzymes, including CYP1A2, CYP2D6 and CYP3A4. In terms of overall ondansetron turnover, CYP3A4 played the predominant role. Because of the multiplicity of metabolic enzymes capable of metabolising ondansetron, it is likely that inhibition or loss of one enzyme (e.g. CYP2D6 enzyme deficiency) will be compensated by others and may result in little change in overall rates of ondansetron clearance.

Pharmacokinetics

Pharmacokinetic studies in human volunteers showed peak plasma levels of 20-30 ng/mL at around 1½ hours after an 8 mg oral dose of ondansetron. An 8 mg infusion of ondansetron resulted in peak plasma levels of 80-100 ng/mL. Repeat dosing of an 8 mg tablet every 8 hours for 6 days increased the peak

plasma value to 40 ng/mL. A continuous intravenous infusion of 1 mg/hour after the initial 8 mg loading dose of ondansetron maintained plasma levels over 30 ng/mL during the following 24-hour period.

The absolute bioavailability of ondansetron in humans was approximately 60% and the plasma protein binding was approximately 73%.

Following oral or IV administration, ondansetron is extensively metabolised and excreted in the urine and faeces. In humans, less than 10% of the dose is excreted unchanged in the urine. The major urinary metabolites are glucuronide conjugates (45%), sulphate conjugates (20%) and hydroxylation products (10%).

The half-life of ondansetron after either an 8 mg oral dose or intravenous dose was approximately 3-4 hours and may be extended to 6-8 hours in the elderly.

Recommended Dose and Dosage Adjustment

Chemotherapy Induced Nausea and Vomiting:

Use in Adults:

Highly Emetogenic Chemotherapy (e.g. regimens containing cisplatin)

Initial Dose for Prevention of Emesis during the First 24 h Following Chemotherapy:

Ondansetron Injection BP (ondansetron hydrochloride) should be given as an initial dose prior to chemotherapy, followed by a dosage regimen tailored to the anticipated severity of emetic response caused by different cancer treatments. The usual dose is Ondansetron Injection BP 8 mg infused intravenously over 15 minutes given at least 30 minutes prior to chemotherapy. A maximum initial dose of Ondansetron Injection BP16 mg IV infused over 15 minutes may be used. A single IV dose greater than 16 mg should not be given due to the dose dependent risk of QTc prolongation. The QTc prolongation effect of Ondansetron Injection IV is also expected to be greater if the drug is administered rapidly. Do not administer more rapidly than the recommended 15-minute infusion.General, QTc Interval Prolongation;

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. IV doses of 8 mg or less do not need to be diluted and may be administered as an IV injection over 15 minutes.

Post-chemotherapy:

Two additional doses of Ondansetron Injection BP 8 mg IV (15 minutes infusions) may be given 4 and 8i hours after the initial dose of Ondansetron Injection BP. After the first 24 hours, Ondansetron 8 mg may be taken orally every 8i hours for up to 5 days.

Less Emetogenic Chemotherapy (e.g. regimens containing cyclophosphamide, doxorubicin, epirubicin, fluorouracil and carboplatin)

Initial Dose:

Ondansetron Injection BP 8 mg infused intravenously over 15 minutes, given at least 30 minutes prior to chemotherapy; or Ondansetron 8 mg orally 1 to 2 hours prior to chemotherapy.

Post-chemotherapy:

Ondansetron 8 mg orally twice daily for up to 5 days.

Use in Children:

Clinical experience of ondansetron hydrochloride for the treatment of Post-Chemotherapy Induced Nausea and Vomiting in children is currently limited, however, ondansetron hydrochloride was effective and well tolerated when given to children 4-12 years of age. Ondansetron Injection BP should be given intravenously at a dose of 3-5 mg/m2 over 15 minutes at least 30 minutes before chemotherapy. For children 3 years of age and younger, there is insufficient information available to make dosage recommendations, therefore, Ondansetron Injection BP is not indicated for the treatment of children 3 years of age or younger.

Use in Elderly:

IV Formulation: In patients 65 years of age or older, all IV doses should be diluted in 50 mL to 100 mL of 0.9% Sodium Chloride Injection or 5% Dextrose Injection.

In patients 65 to 74 years of age, the initial IV dose of Ondansetron Injection BP 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. When the initial dose is 16 mg, there is a predicted increase of the risk for a slight QTcF interval prolongation above 10 ms (from baseline) for about 10 min. ECG monitoring may be considered.

In patients 75 years of age or older, the initial IV dose of Ondansetron Injection BP 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. For the third dose, there is a i The efficacy of twice daily dosage regimens for the treatment of post-chemotherapy emesis has been established only in adult patients receiving less emetogenic chemotherapy. The appropriateness of twice versus three times daily dosage regimens for other patient groups should be based on an assessment of the needs and responsiveness of the individual patientpredicted increase of the risk for a slight QTcF interval prolongation above 10 ms (from baseline) for about 10 min. ECG monitoring may be considered.

Post-Operative Nausea and Vomiting:

Use in Adults: For prevention of post-operative nausea and vomiting Ondansetron may be administered as a single dose of 16 mg given orally one hour prior to anaesthesia. Alternatively, a single dose of 4 mg, undiluted may be injected intravenously preferably over 2-5 minutes, and not less than 30 seconds, at induction of anaesthesia. For the treatment of established post-operative nausea and vomiting, a single dose of 4 mg, undiluted injected intravenously preferably over 2-5 minutes, and not less than 30 seconds, is recommended.

Use in Children:

There is no experience in the use of ondansetron hydrochloride in the prevention and treatment of post-operative nausea and vomiting in children. Ondansetron Injection BP is not indicated for this use in children.

Use in Elderly:

There is limited experience in the use of ondansetron hydrochloride in the prevention and treatment of post-operative nausea and vomiting in the elderly. Ondansetron Injection BP is not indicated for this use in the elderly.