EMESET Injection (Ondansetron hydrochloride)

**Composition**

EMESET Injection (2 ml and 4 ml)
Each ml contains:
Ondansetron Hydrochloride equivalent to Ondansetron ...................... 2 mg
Water for Injection IP ......................... Q.s.

**Dosage Form**

Injection for intravenous or intramuscular use

**Pharmacology**

**Pharmacodynamics**

Ondansetron is a selective 5-HT<sub>3</sub>-receptor antagonist. While ondansetron's mechanism of action has not been fully characterized, it is not a dopamine-receptor antagonist.

QTc interval prolongation was studied in a double blind, single intravenous dose, placebo- and positive-controlled, crossover study in 58 healthy subjects. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline-correction was 19.5 (21.8) ms and 5.6 (7.4) ms after 15 minute intravenous infusions of 32 mg and 8 mg ondansetron Injection, USP, respectively. A significant exposure-response relationship was identified between ondansetron concentration and ΔΔQTcF. Using the established exposure-response relationship, 24 mg infused intravenously over 15 min had a mean predicted (95% upper prediction interval) ΔΔQTcF of 14.0 (16.3) ms. In contrast, 16 mg infused intravenously over 15 min using the same model had a mean predicted (95% upper prediction interval) ΔΔQTcF of 9.1 (11.2) ms.

In normal volunteers, single intravenous doses of 0.15 mg/kg of ondansetron had no effect on esophageal motility, gastric motility, lower esophageal sphincter pressure, or small intestinal transit time. In another study in 6 normal male volunteers, a 16-mg dose infused over 5 minutes showed no effect of the drug on cardiac output, heart rate, stroke volume, blood pressure, or electrocardiogram (ECG). Multiday administration of ondansetron has been shown to slow colonic transit in normal volunteers. Ondansetron has no effect on plasma prolactin concentrations.

In a gender-balanced pharmacodynamic study (n = 56), ondansetron 4 mg administered intravenously or intramuscularly was dynamically similar in the prevention of nausea and vomiting using the ipecacuanha model of emesis.
Pharmacokinetics

In normal adult volunteers, the following mean pharmacokinetic data have been determined following a single 0.15mg/kg intravenous dose.

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>n</th>
<th>Peak Plasma Concentration (ng/mL)</th>
<th>Mean Elimination Half-life (h)</th>
<th>Plasma Clearance (L/h/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19-40</td>
<td>11</td>
<td>102</td>
<td>3.5</td>
<td>0.381</td>
</tr>
<tr>
<td>61-74</td>
<td>12</td>
<td>106</td>
<td>4.7</td>
<td>0.319</td>
</tr>
<tr>
<td>≥75</td>
<td>11</td>
<td>170</td>
<td>5.5</td>
<td>0.262</td>
</tr>
</tbody>
</table>

Absorption
A study was performed in normal volunteers (n = 56) to evaluate the pharmacokinetics of a single 4mg dose administered as a 5-minute infusion compared to a single intramuscular injection. Systemic exposure as measured by mean AUC were equivalent, with values of 156 (95% CI, 136, 180) and 161 (95% CI, 137, 190)ng·h/mL for the intravenous and intramuscular groups, respectively. Mean peak plasma concentrations were 42.9 (95% CI, 33.8, 54.4)ng/mL at 10 minutes after intravenous infusion and 31.9 (95% CI, 26.3, 38.6)ng/mL at 41 minutes after intramuscular injection.

Distribution
Plasma protein binding of ondansetron as measured in vitro was 70% to 76%, over the pharmacologic concentration range of 10 to 500 ng/mL. Circulating drug also distributes into erythrocytes.

Metabolism
Ondansetron is extensively metabolized in humans, with approximately 5% of a radiolabelled dose recovered as the parent compound from the urine. The primary metabolic pathway is hydroxylation on the indole ring followed by subsequent glucuronide or sulphate conjugation.

Although some non-conjugated metabolites have pharmacologic activity, these are not found in plasma at concentrations likely to significantly contribute to the biological activity of ondansetron. The metabolites are observed in the urine.

*In vitro* metabolism studies have shown that ondansetron is a substrate for multiple human hepatic cytochrome (CY) P450 enzymes, including CYP1A2, CYP2D6 and CYP3A4. In terms of overall ondansetron turnover, CYP3A4 plays a predominant role while formation of the major in vivo metabolites is apparently mediated by CYP1A2. The role of CYP2D6 in ondansetron in vivo metabolism is relatively minor.

The pharmacokinetics of intravenous ondansetron did not differ between subjects who were poor metabolizers of CYP2D6 and those who were extensive metabolizers of CYP2D6, further supporting the limited role of CYP2D6 in
ondansetron disposition in vivo.

Elimination
In adult cancer patients, the mean ondansetron elimination half-life was 4.0 hours, and there was no difference in the multi-dose pharmacokinetics over a 4-day period. In a dose-proportionality study, systemic exposure to 32 mg of ondansetron was not proportional to dose as measured by comparing dose-normalized AUC values to an 8mg dose. This is consistent with a small decrease in systemic clearance with increasing plasma concentrations.

Special Populations

Geriatric
A reduction in clearance and increase in the elimination half-life are seen in patients over 75 years of age. In clinical trials with cancer patients, safety and efficacy were similar in patients over 65 years of age and those under 65 years of age; there was an insufficient number of patients over 75 years of age to permit conclusions in that age group. No dosage adjustment is recommended in the elderly.

Paediatric
Pharmacokinetic samples were collected from 74 cancer patients (6 to 48 months of age) who received a dose of 0.15 mg/kg of intravenous ondansetron every 4 hours (totally three doses) during a safety and efficacy trial. These data were combined with sequential pharmacokinetics data from 41 surgery patients (1 month to 24 months of age) who received a single dose of 0.1 mg/kg of intravenous ondansetron prior to surgery with general anaesthesia, and a population pharmacokinetic analysis was performed on the combined data set. The results of this analysis are included in Table 2 and are compared to the pharmacokinetic results in cancer patients (4 to 18 years of age).

<table>
<thead>
<tr>
<th>Subjects and Age Group</th>
<th>n</th>
<th>CL (L/h/kg)</th>
<th>Vdss (L/kg)</th>
<th>T½ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 to 18 years of age</td>
<td>21</td>
<td>0.599</td>
<td>1.9</td>
<td>2.8</td>
</tr>
<tr>
<td>1 month to 48 months of age</td>
<td>115</td>
<td>0.582</td>
<td>3.65</td>
<td>4.9</td>
</tr>
</tbody>
</table>

*Population pharmacokinetic patients: 64% cancer patients and 36% surgery patients.*

Based on the population pharmacokinetic analysis, cancer patients (6 to 48 months of age) who receive a dose of 0.15 mg/kg of intravenous ondansetron every 4 hours for three doses would be expected to achieve a systemic exposure (AUC) consistent with the exposure achieved in previous paediatric studies in cancer patients (4 to 18 years of age) at similar doses.

In a study of 21 paediatric patients (3 to 12 years of age) who were undergoing surgery requiring anaesthesia for a duration of 45 minutes to 2 hours, a single intravenous dose of ondansetron, 2 mg (3 to 7 years of age) or 4 mg (8 to 12 years of age), was administered immediately prior to anaesthesia induction. Mean weight-normalized clearance and volume of distribution values in these paediatric surgical patients were similar to those previously reported for young
adults. Mean terminal half-life was slightly reduced in paediatric patients (range: 2.5 to 3 hours) in comparison with adults (range: 3 to 3.5 hours).

In a study of 51 paediatric patients (1 month to 24 months of age) who were undergoing surgery requiring general anaesthesia, a single intravenous dose of ondansetron, 0.1 or 0.2 mg/kg, was administered prior to surgery. As shown in Table 3, the 41 patients with pharmacokinetic data were divided into two groups—patients, 1 month to 4 months of age, and patients, 5 to 24 months of age—and are compared to paediatric patients (3 to 12 years of age).

### Table 3: Pharmacokinetics in Paediatric Surgery Patients, 1 Month to 12 Years of Age

<table>
<thead>
<tr>
<th>Subjects and Age Group</th>
<th>n</th>
<th>CL (L/h/kg)</th>
<th>Vdss (L/kg)</th>
<th>T½ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Geometric Mean</td>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td>Paediatric surgery patients</td>
<td>n = 21</td>
<td>0.439</td>
<td>1.65</td>
<td>2.9</td>
</tr>
<tr>
<td>3 to 12 years of age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paediatric surgery patients</td>
<td>n = 22</td>
<td>0.581</td>
<td>2.3</td>
<td>2.9</td>
</tr>
<tr>
<td>5 to 24 months of age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paediatric surgery patients</td>
<td>n = 19</td>
<td>0.401</td>
<td>3.5</td>
<td>6.7</td>
</tr>
<tr>
<td>1 month to 4 months of age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In general, surgical and cancer paediatric patients younger than 18 years tend to have a higher ondansetron clearance compared to adults, leading to a shorter half-life in most paediatric patients. In patients who were 1 month to 4 months of age, a longer half-life was observed due to the higher volume of distribution in this age group.

In a study of 21 paediatric cancer patients (4 to 18 years of age) who received three intravenous doses of 0.15 mg/kg of ondansetron at 4-hour intervals, patients older than 15 years exhibited ondansetron pharmacokinetic parameters similar to those of adults.

**Renal Impairment**

Due to the very small contribution (5%) of renal clearance to the overall clearance, renal impairment was not expected to significantly influence the total clearance of ondansetron. However, ondansetron mean plasma clearance was reduced by about 41% in patients with severe renal impairment (creatinine clearance

**Hepatic Impairment**

In patients with mild-to-moderate hepatic impairment, the clearance is reduced 2-fold and the mean half-life is increased to 11.6 hours compared to 5.7 hours in normals. In patients with severe hepatic impairment (Child-Pugh score of 10 or greater), clearance is reduced 2-fold to 3-fold and the apparent volume of distribution is increased, with a resultant increase in half-life to 20 hours. In patients with severe hepatic impairment, a total daily dose of 8 mg should not be exceeded.
Indications

Prevention of Nausea and Vomiting Associated with Initial and Repeat Courses of Emetogenic Cancer Chemotherapy

Ondansetron Injection is indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin. Ondansetron is approved for patients aged 6 months and older.

Prevention of Post-Operative Nausea and/or Vomiting

Ondansetron Injection is indicated for the prevention of post-operative nausea and/or vomiting. As with other anti-emetics, routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and/or vomiting will occur post-operatively. In patients in whom nausea and/or vomiting must be avoided post-operatively, ondansetron injection is recommended even when the incidence of post-operative nausea and/or vomiting is low. For patients who do not receive prophylactic ondansetron injection and experience nausea and/or vomiting post-operatively, ondansetron injection may be given to prevent further episodes. Ondansetron is approved for patients aged 1 month and older.

Dosage And Administration

Prevention of Nausea and Vomiting Associated with Initial and Repeat Courses of Emetogenic Chemotherapy

Ondansetron Injection should be diluted in 50 ml of 5% Dextrose Injection or 0.9% Sodium Chloride Injection before administration.

Adults
The recommended adult intravenous dosage of ondansetron is three 0.15mg/kg doses up to a maximum of 16 mg per dose. The first dose is infused over 15 minutes, beginning 30 minutes before the start of emetogenic chemotherapy. Subsequent doses (0.15 mg/kg up to a maximum of 16 mg per dose) are administered 4 and 8 hours after the first dose of ondansetron.

Paediatric Use
For paediatric patients (6 months through 18 years of age), the intravenous dosage of ondansetron is three 0.15mg/kg doses up to a maximum of 16 mg per dose. The first dose is to be administered 30 minutes before the start of moderately-to-highly emetogenic chemotherapy. Subsequent doses (0.15 mg/kg up to a maximum of 16 mg per dose) are administered 4 and 8 hours after the first dose of ondansetron. The drug should be infused intravenously over 15 minutes.

Prevention of Post-Operative Nausea and Vomiting

Ondansetron injection should not be mixed with solutions for which physical and chemical compatibility have not been established. In particular, this applies to alkaline solutions as a precipitate may form.
Adults
The recommended adult intravenous dosage of ondansetron is 4 mg undiluted, administered intravenously in not less than 30 seconds, preferably over 2 to 5 minutes, immediately before the induction of anaesthesia, or post-operatively if the patient did not receive prophylactic anti-emetics and experiences nausea and/or vomiting within 2 hours after surgery. Alternatively, 4 mg undiluted may be administered intramuscularly as a single injection for adults. While recommended as a fixed dose for patients weighing more than 40 kg, few patients above 80 kg have been studied.

In patients who do not achieve adequate control of post-operative nausea and vomiting following a single, prophylactic, pre-induction, intravenous dose of ondansetron 4 mg, administration of a second intravenous dose of 4 mg ondansetron post-operatively does not provide additional control of nausea and vomiting.

Paediatric Use
For paediatric patients 1 month through 12 years of age, the dosage is a single 0.1mg/kg dose for patients weighing 40 kg or less, or a single 4mg dose for patients weighing more than 40 kg. The rate of administration should not be less than 30 seconds, preferably over 2 to 5 minutes immediately prior to or following anaesthesia induction, or post-operatively if the patient did not receive prophylactic anti-emetics and experiences nausea and/or vomiting shortly after surgery. Prevention of further nausea and vomiting was only studied in patients who had not received prophylactic ondansetron.

Dosage Adjustment for Patients with Impaired Hepatic Function
In patients with severe hepatic impairment (Child-Pugh score of 10 or greater), a single maximal daily dose of 8 mg infused over 15 minutes, beginning 30 minutes before the start of the emetogenic chemotherapy, is recommended. There is no experience beyond first-day administration of ondansetron in these patients.

Note:
After dilution, do not use beyond 24 hours. Although Ondansetron Injection is chemically and physically stable when diluted as recommended, sterile precautions should be observed because diluents generally do not contain preservative.

Ondansetron Injection is stable at room temperature under normal lighting conditions for 48 hours after dilution with the following intravenous fluids: 0.9% Sodium Chloride Injection, 5% Dextrose Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, 5% Dextrose and 0.45% Sodium Chloride Injection, and 3% Sodium Chloride Injection.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

Precaution: Occasionally, ondansetron precipitates at the stopper/vial interface in vials stored upright. Potency and safety are not affected. If a precipitate is observed, resolubilize by shaking the vial vigorously.

Contraindications
Ondansetron injection is contraindicated for patients known to have a hypersensitivity (e.g., anaphylaxis) to this product or any of its components. Anaphylactic reactions have been reported in patients taking ondansetron.
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.

### Warnings And Precautions

#### Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis and bronchospasm, have been reported in patients who have exhibited hypersensitivity to other selective 5-HT$_3$-receptor antagonists.

#### QT Prolongation

Ondansetron prolongs the QT interval in a dose-dependent manner. In addition, post-marketing cases of *torsades de pointes* have been reported in patients using ondansetron. Avoid Ondansetron in patients with congenital long-QT syndrome. ECG monitoring is recommended in patients with electrolyte abnormalities (e.g., hypokalaemia or hypomagnesaemia), congestive heart failure, bradyarrhythmias, or patients taking other medicinal products that lead to QT prolongation.

#### Masking of Progressive Ileus and Gastric Distension

The use of ondansetron in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and gastric distention.

#### Effect on Peristalsis

Ondansetron is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction.

### Drug Interactions

#### Drugs Affecting CYP450 Enzymes

Ondansetron does not appear to induce or inhibit the CYP450 drug-metabolizing enzyme system of the liver. Because ondansetron is metabolized by hepatic CYP450 drug-metabolizing enzymes (CYP3A4, CYP2D6, CYP1A2), inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of ondansetron. On the basis of available data, no dosage adjustment is recommended for patients on these drugs.

#### Apomorphine

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

#### Phenytoin, Carbamazepine and Rifampicin
In patients treated with potent inducers of CYP3A4 (i.e., phenytoin, carbamazepine and rifampicin), the clearance of ondansetron was significantly increased and ondansetron blood concentrations were decreased. However, on the basis of available data, no dosage adjustment for ondansetron is recommended for patients on these drugs.

Tramadol
Although no pharmacokinetic drug interaction between ondansetron and tramadol has been observed, data from two small studies indicate that ondansetron may be associated with an increase in patient-controlled administration of tramadol.

Chemotherapy
In humans, carmustine, etoposide and cisplatin do not affect the pharmacokinetics of ondansetron.

In a crossover study in 76 paediatric patients, intravenous ondansetron did not increase blood levels of high-dose methotrexate.

Temazepam
The co-administration of ondansetron had no effect on the pharmacokinetics and pharmacodynamics of temazepam.

Alfentanil and Atracurium
Ondansetron does not alter the respiratory depressant effects produced by alfentanil or the degree of neuromuscular blockade produced by atracurium. Interactions with general or local anaesthetics have not been studied.

### Pregnancy

**Pregnancy Category B**
Reproduction studies have been performed in pregnant rats and rabbits at intravenous doses up to 4 mg/kg per day (approximately 1.4 and 2.9 times the recommended human intravenous dose of 0.15 mg/kg given three times a day, respectively, based on body surface area) and have revealed no evidence of impaired fertility or harm to the foetus due to ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

### Lactation

Ondansetron is excreted in the breast milk of rats. It is not known whether ondansetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ondansetron is administered to a nursing mother.

### Paediatric Use

Little information is available about the use of ondansetron in paediatric surgical patients younger than 1 month of age. Little information is available about the use of ondansetron in paediatric cancer patients younger than 6 months of age.
The clearance of ondansetron in paediatric patients, 1 month to 4 months of age, is slower and the half-life is ~2.5-fold longer than patients who are >4 to 24 months of age. As a precaution, it is recommended that patients less than 4 months of age receiving this drug be closely monitored.

### Geriatric Use

Of the total number of subjects enrolled in cancer chemotherapy-induced and post-operative nausea and vomiting in U.S. trials and foreign-controlled clinical trials, 862 were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but the greater sensitivity of some elderly individuals cannot be ruled out. Dosage adjustment is not needed in patients over the age of 65 years.

### Renal Impairment

Although plasma clearance is reduced in patients with severe renal impairment (creatinine clearance <30 mL/min), no dosage adjustment is recommended.

### Hepatic Impairment

In patients with severe hepatic impairment (Child-Pugh score of 10 or greater), clearance is reduced and the apparent volume of distribution is increased, with a resultant increase in plasma half-life. In such patients, a total daily dose of 8 mg should not be exceeded.

### Undesirable Effects

#### Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The following adverse reactions have been reported in clinical trials of adult patients treated with ondansetron, the active ingredient of intravenous ondansetron, across a range of dosages. A causal relationship to therapy with ondansetron was unclear in many cases.

**Chemotherapy-induced Nausea and Vomiting**

### Table 4: Adverse Reactions Reported in >5% of Adult Patients Who Received Ondansetron at a Dosage of Three 0.15mg/kg Doses
Cardiovascular: Rare cases of angina (chest pain), ECG alterations, hypotension, and tachycardia have been reported.

Gastrointestinal: Constipation has been reported in 11% of chemotherapy patients receiving multiday ondansetron.

Hepatic: In comparative trials in cisplatin chemotherapy patients with normal baseline values of aspartate transaminase (AST) and alanine transaminase (ALT), these enzymes have been reported to exceed twice the upper limit of normal in approximately 5% of patients. The increases were transient and did not appear to be related to dose or duration of therapy. On repeat exposure, similar transient elevations in transaminase values occurred in some courses, but symptomatic hepatic disease did not occur.

Integumentary: Rash has occurred in approximately 1% of patients receiving ondansetron.

Neurological: There have been rare reports consistent with, but not diagnostic of, extra-pyramidal reactions in patients receiving ondansetron injection, and rare cases of grand mal seizure.

Other: Rare cases of hypokalaemia have been reported.

Post-Operative Nausea and Vomiting

*Adults*

The adverse reactions in Table 5 have been reported in ≥2% of adults receiving ondansetron at a dosage of 4 mg intravenous over 2 to 5 minutes in clinical trials.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Number of Adult Patients with Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ondansetron Injection</td>
</tr>
<tr>
<td></td>
<td>0.15 mg/kg × 3</td>
</tr>
<tr>
<td></td>
<td>n = 419</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>16%</td>
</tr>
<tr>
<td>Headache</td>
<td>17%</td>
</tr>
<tr>
<td>Fever</td>
<td>8%</td>
</tr>
</tbody>
</table>

Table 5: Adverse Reactions Reported in ≥2% (and with Greater Frequency than the Placebo Group) of Adult Patients Receiving Ondansetron at a Dosage of 4 mg Intravenous over 2 to 5 Minutes
### Cold sensation

<table>
<thead>
<tr>
<th></th>
<th>Ondansetron</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold sensation</td>
<td>9 (2%)</td>
<td>8 (1%)</td>
</tr>
</tbody>
</table>

### Pruritus

<table>
<thead>
<tr>
<th></th>
<th>Ondansetron</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>9 (2%)</td>
<td>3 (&lt;1%)</td>
</tr>
</tbody>
</table>

### Paraesthesia

<table>
<thead>
<tr>
<th></th>
<th>Ondansetron</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraesthesia</td>
<td>9 (2%)</td>
<td>2 (&lt;1%)</td>
</tr>
</tbody>
</table>

* Adverse reactions: Rates of these reactions were not significantly different in the ondansetron and placebo groups.

* Patients were receiving multiple concomitant peri-operative and post-operative medications.

#### Paediatric

Rates of adverse reactions were similar in both the ondansetron and placebo groups in paediatric patients receiving ondansetron (a single 0.1mg/kg dose for paediatric patients weighing 40 kg or less, or 4 mg for paediatric patients weighing more than 40 kg) administered intravenously over at least 30 seconds. Diarrhoea was seen more frequently in patients taking ondansetron (2%) compared to placebo (1 month to 24 month age group. These patients were receiving multiple concomitant peri-operative and post-operative medications.

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#### Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ondansetron. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to ondansetron.

**Cardiovascular:** Arrhythmias (including ventricular and supraventricular tachycardia, premature ventricular contractions, and atrial fibrillation), bradycardia, ECG alterations (including second-degree heart block, QT interval prolongation, and ST segment depression), palpitations, and syncope. Rarely and predominantly with intravenous ondansetron, transient ECG changes, including QT/QTc interval prolongation, have been reported.

**General:** Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylaxis/anaphylactoid reactions, angio-oedema, bronchospasm, cardiopulmonary arrest, hypotension, laryngeal oedema, laryngospasm, shock, shortness of breath, stridor) have also been reported. A positive-lymphocyte transformation test to ondansetron has been reported, which suggests immunologic sensitivity to ondansetron.

**Hepatobiliary:** Liver enzyme abnormalities have been reported. Liver failure and death have been reported in patients with cancer receiving concurrent medications, including potentially hepatotoxic cytotoxic chemotherapy and antibiotics.

**Local Reactions:** Pain, redness and burning at the site of injection.

**Lower Respiratory:** Hiccups.

**Neurological:** Oculogyric crisis, appearing alone, as well as with other dystonic reactions.

**Skin:** Urticaria.

**Eye Disorders:** Cases of transient blindness, predominantly during intravenous administration, have been reported. These cases of transient blindness were reported to resolve within a few minutes up to 48 hours. Transient blurred vision, in some cases associated with abnormalities of accommodation, has also been reported.
Overdosage

There is no specific antidote for ondansetron overdose. Patients should be managed with appropriate supportive therapy. Individual doses as large as 150 mg and total daily dosages (three doses) as large as 252 mg have been administered intravenously without significant adverse events. These doses are more than 10 times the recommended daily dose.

In addition to the adverse events listed above, the following events have been described in the setting of ondansetron overdose: ‘sudden blindness' (amaurosis) of 2 to 3 minutes' duration plus severe constipation occurred in a patient who was administered 72 mg of ondansetron intravenously as a single dose. Hypotension (and faintness) occurred in another patient who took 48 mg of oral ondansetron. Following infusion of 32 mg over only a 4-minute period, a vasovagal episode with transient second-degree heart block was observed. In all instances, the events resolved completely.

Storage And Handling Instructions

Store in a cool place. Protect from light. Do not freeze.

Packaging Information

EMESET Injection: Ampoules of 2 ml and 4 ml

Last updated: November 2013
Last reviewed: November 2013

EMESET Injection

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