Ondansetron
Zofran®
Tablet
Anti emetic

PRODUCT DESCRIPTION
Each yellow, oval, film coated tablet engraved with 'GX ET5' contains 8mg ondansetron (as hydrochloride dihydrate).

PHARMACOLOGICAL PROPERTIES
Pharmacodynamics
Mechanism of Action
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.

Pharmacodynamic Effects
Ondansetron does not alter plasma prolactin concentrations.

QT Prolongation
The effect of ondansetron on the QTc interval was evaluated in a double blind, randomized, placebo and positive (moxifloxacin) controlled, crossover study in 58 healthy adult men and women. Ondansetron doses included 8 mg and 32 mg infused intravenously over 15 minutes. At the highest tested dose of 32 mg, the maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction was 19.6 (21.5) msec. At the lower tested dose of 8 mg, the maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction was 5.8 (7.8) msec. In this study, there were no QTcF measurements greater than 480 msec and no QTcF prolongation was greater than 60 msec.

Pharmacokinetics
The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

Absorption
Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism. Peak plasma concentrations are attained approximately 1.5 hours after dosing. For doses above 8 mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher oral doses. Mean bioavailability in healthy male subjects, following the administration of a single 8 mg tablet, is approximately 55 to 60%. Bioavailability is slightly enhanced by the presence of food but unaffected by antacids.

Distribution
Ondansetron is not highly protein bound (70 to 76%).
The disposition of ondansetron following oral, IM or IV dosing in adults is similar with a steady state volume of distribution of about 140 L.

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.

Elimination
Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism. Less than 5% of the absorbed dose is excreted unchanged in the urine.
The disposition of ondansetron following oral, IM or IV dosing is similar with a terminal elimination half - life of about 3 hours.

Special Patient Populations
- Gender
  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).
- Children and Adolescents (aged 1 month to 17 years)
  In paediatric patients aged 1 to 4 months (n=19) undergoing surgery, weight-normalised clearance was approximately 30% slower than in patients aged 5 to 24 months (n=22) 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. The differences in pharmacokinetic parameters in the 1 to 4 month patient population can be explained in part by the higher percentage of total body water in neonates and infants and a higher volume of distribution for water soluble drugs like ondansetron.
  In paediatric patients aged 3 to 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron 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 compensates for age-related changes and is effective in normalising systemic exposure in paediatric patients. Population pharmacokinetic analysis was performed on 428 subjects (cancer patients, surgery patients and healthy volunteers) aged 1 month to 44 years following IV administration of ondansetron. Based on this analysis, systemic exposure (AUC) of ondansetron following oral or IV dosing in children and adolescents was comparable to adults, with the exception of infants aged 1 to 4 months. Volume of distribution was related to age and was lower in infants than in children. Clearance was related to weight but not to age with the exception of infants aged 1 to 4 months. It is difficult to conclude whether there was an additional reduction in clearance related to age in infants 1 to 4 months or simply inherent variability due to the low number of subjects studied in this age group. Since patients less than 6 months of age will only receive a single dose in PONV a decreased clearance is not likely to be clinically relevant.

- **Elderly**
  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.

- **Renal Impairment**
  In patients with moderate renal impairment (creatinine clearance 15 to 60 mL/min), both systemic clearance and volume of distribution are reduced following IV administration of ondansetron, resulting in a slight, but clinically insignificant, increase in elimination half-life (5.4 hours). A study in patients with severe renal impairment who required regular haemodialysis (studied between dialyses) showed ondansetron's pharmacokinetics to be essentially unchanged following IV administration.

- **Hepatic Impairment**
  In patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced with prolonged elimination half-lives (15 to 32 hours) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism.

**Pre-clinical 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 at clinically relevant concentrations. Dose-dependent QT prolongation has been observed in a thorough QT study in human volunteers (see Pharmacodynamic Effects – QT prolongation).

**INDICATIONS**

**Adults**
Ondansetron (Zofran®) oral formulations are indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.
Ondansetron (Zofran®) is also indicated for the prevention of post-operative nausea and vomiting.

**Paediatric Population**

**Injection and oral formulations:**
Ondansetron (Zofran®) is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy. No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of post-operative nausea and vomiting: IV injection is recommended for this purpose.

**DOSAGE AND ADMINISTRATION**
Ondansetron (Zofran®) is available for oral, parenteral and rectal use to allow the route of administration and dosing to be flexible.

**CHEMOTHERAPY AND RADIOTHERAPY INDUCED NAUSEA AND VOMITING (CINV and RINV)**
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.

**Populations**

- **CINV and RINV in Adults**
The recommended oral dose is 8 mg taken 1 to 2 hours before chemotherapy or radiation treatment, followed by 8 mg orally every 12 hours for a maximum of 5 days.

- **CINV in Children and Adolescents (aged 6 months to 17 years)**
The recommended oral dose is 8 mg taken 1 to 2 hours before chemotherapy, may be used. After the first 24 hours, oral or rectal treatment with Ondansetron (Zofran®) may be continued for up to 5 days after a course of treatment. The recommended oral dose is 8 mg to be taken twice daily.

**Dosing by BSA**
Ondansetron (Zofran®) should be administered immediately before chemotherapy as a single IV dose of 5 mg/m². The IV dose must not exceed 8 mg. Oral dosing can commence 12 hours later and may be continued for up to 5 days (Table 1). Adult doses must not be exceeded.
Table 1. BSA-based dosing for CINV (aged 6 months to 17 years)

<table>
<thead>
<tr>
<th>BSA</th>
<th>Day 1</th>
<th>Days 2 - 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.6 m²</td>
<td>5 mg/m² IV plus 2 mg syrup after 12 hours</td>
<td>2 mg syrup every 12 hours</td>
</tr>
<tr>
<td>≥ 0.6 m² to &lt; 1.2 m²</td>
<td>5 mg/m² IV plus 4 mg syrup or tablet after 12 hours</td>
<td>4 mg syrup or tablet every 12 hours</td>
</tr>
<tr>
<td>&gt; 1.2 m²</td>
<td>5 mg/m² IV or 8 mg IV plus 8 mg syrup or tablet after 12 hours</td>
<td>8 mg syrup or tablet every 12 hours</td>
</tr>
</tbody>
</table>

Dosing by body weight

Ondansetron (Zofran®) should be administered immediately before chemotherapy as a single IV dose of 0.15 mg/kg. The IV dose must not exceed 8 mg. On Day 1, two further IV doses may be given in 4-hourly intervals. Oral dosing can commence 12 hours later and may be continued for up to 5 days (Table 2). Adult doses must not be exceeded.

Table 2. Weight-based dosing for CINV (aged 6 months to 17 years)

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Day 1</th>
<th>Days 2 - 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10 kg</td>
<td>Up to 3 doses of 0.15 mg/kg IV every 4 hours</td>
<td>2 mg syrup every 12 hours</td>
</tr>
<tr>
<td>&gt; 10 kg</td>
<td>Up to 3 doses of 0.15 mg/kg IV every 4 hours</td>
<td>4 mg syrup or tablet every 12 hours</td>
</tr>
</tbody>
</table>

- CINV and RINV in Elderly
  No alteration of oral dose or frequency of administration is required.
- 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)

- PONV in Adults
  For prevention of post-operative nausea and vomiting, the recommended oral dose is 16 mg given 1 hour prior to anaesthesia. For treatment of established post-operative nausea and vomiting, Ondansetron (Zofran®) administration by injection is recommended.
- PONV in Children and Adolescents (aged 1 month to 17 years)
  No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of post-operative nausea and vomiting; slow IV injection (not less than 30 seconds) is recommended for this purpose.
- Elderly
  There is limited experience in the use of Ondansetron (Zofran®) in the prevention and treatment of post-operative nausea and vomiting in the elderly, however Ondansetron (Zofran®) 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.

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 preparation.

WARNINGS AND PRECAUTIONS

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

Ondansetron prolongs the QT interval in a dose-dependent manner (see Pharmacodynamic Effects). 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 Ondansetron (Zofran®) and other serotonergic drugs (see Interactions). If concomitant treatment with Ondansetron (Zofran®) and other serotonergic drugs is clinically warranted, appropriate observation of the patient is advised.

As Ondansetron (Zofran®) is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration.

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

In psychomotor testing Ondansetron (Zofran®) does not impair performance nor cause sedation. No detrimental effects on such activities are predicted from the pharmacology of Ondansetron (Zofran®).

**DRUG INTERACTIONS**

There is no evidence that Ondansetron (Zofran®) 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 (Zofran®) is administered with alcohol, temazepam, furosemide, 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.

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

**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**

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.

**Serotonergic Drugs (e.g., SSRIs and SNRIs)**

Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been described following the concomitant use of Ondansetron (Zofran®) and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs) (see Warnings and Precautions).

**Tramadol**

Data from small studies indicate that Ondansetron (Zofran®) may reduce the analgesic effect of tramadol.

**PREGNANCY AND LACTATION**

**Pregnancy**

The safety of Ondansetron (Zofran®) 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 (Zofran®) 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 (Zofran®) should not breast-feed their babies.

**ADVERSE EFFECTS**

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); and very rare (<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 (Zofran®) according to indication and formulation. The adverse event profiles in children and adolescents were comparable to that seen in adults.

**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 dystonic reactions, oculogyric crisis and dyskinesia) have been observed without definitive evidence of persistent clinical sequelae.

Rare: Dizziness predominantly during rapid IV administration.

**Eye disorders**

Rare: Transient visual disturbances (e.g. blurred vision) predominantly during IV 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.

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.
Local burning sensation following insertion of suppositories.

**Hepatobiliary disorders**
Uncommon: Asymptomatic increases in liver function tests.
*These events were observed commonly 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 IV injection site reactions.

**OVERDOSAGE AND TREATMENT**

**Symptoms and Signs**
There is limited experience of Ondansetron (Zofran®) overdose. In the majority of cases symptoms were similar to those already reported in patients receiving recommended doses (see Adverse Reactions). Ondansetron prolongs QT interval in a dose-dependent fashion. ECG monitoring is recommended in cases of overdose.

**Treatment**
There is no specific antidote for Ondansetron (Zofran®), therefore in cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.
The use of ipecacuanha to treat overdose with Ondansetron (Zofran®) is not recommended as patients are unlikely to respond due to the anti-emetic action of ondansetron itself.

**STORAGE CONDITIONS**
Ondansetron (Zofran®) tablets should be stored at temperatures not exceeding 30°C. Protect from light.

**AVAILABILITY**
Ondansetron (Zofran®) 8mg tablet: Box of 10’s

**CAUTION**
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

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Version Number: GDS38/IP113. Revision Date: 3 April 2014
Ondansetron
Zofran
Solution for Injection
Anti emetic

PRODUCT DESCRIPTION
Ondansetron (Zofran®) 2mg/mL Solution for Injection: Each mL of the clear, colourless, sterile solution contains 2mg ondansetron (as hydrochloride dihydrate) in aqueous solution for IM or IV administration.
Each 2mL ampoule contains 4mg ondansetron (as hydrochloride dihydrate) intended for post-operative nausea and vomiting.
Each 4mL ampoule contains 8mg ondansetron (as hydrochloride dihydrate) intended for chemotherapy and radiotherapy induced nausea and vomiting.

PHARMACOLOGIC PROPERTIES
Pharmacodynamics
Mechanism of Action
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.

Pharmacodynamic Effects
Ondansetron does not alter plasma prolactin concentrations.

QT Prolongation
The effect of ondansetron on the QTc interval was evaluated in a double blind, randomized, placebo and positive (moxifloxacin) controlled, crossover study in 58 healthy adult men and women. Ondansetron doses included 8 mg and 32 mg infused intravenously over 15 minutes. At the highest tested dose of 32 mg, the maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction was 19.6 (21.5) msec. At the lower tested dose of 8 mg, the maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction was 5.8 (7.8) msec. In this study, there were no QTcF measurements greater than 480 msec and no QTcF prolongation was greater than 60 msec.

Pharmacokinetics
The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

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

Distribution
Ondansetron is not highly protein bound (70 to 76%).
The disposition of Ondansetron following oral, IM or IV dosing in adults is similar with a steady state volume of distribution of about 140 L.

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.

Elimination
Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism. Less than 5% of the absorbed dose is excreted unchanged in the urine.
The disposition of ondansetron following oral, IM or IV dosing is similar with a terminal elimination half-life of about 3 hours.

Special Patient Populations
- Gender
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).

• Children and Adolescents (aged 1 month to 17 years)
In paediatric patients aged 1 to 4 months (n=19) undergoing surgery, weight-normalised clearance was approximately 30% slower than in patients aged 5 to 24 months (n=22) 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. The differences in pharmacokinetic parameters in the 1 to 4 month patient population can be explained in part by the higher percentage of total body water in neonates and infants and a higher volume of distribution for water soluble drugs like ondansetron.
In paediatric patients aged 3 to 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron 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 compensates for age-related changes and is effective in normalising systemic exposure in paediatric patients. Population pharmacokinetic analysis was performed on 428 subjects (cancer patients, surgery patients and healthy volunteers) aged 1 month to 44 years following IV administration of ondansetron. Based on this analysis, systemic exposure (AUC) of ondansetron following oral or IV dosing in children and adolescents was comparable to adults, with the exception of infants aged 1 to 4 months. Volume of distribution was related to age and was lower in adults than in infants and children. Clearance was related to weight but not to age with the exception of infants aged 1 to 4 months. It is difficult to conclude whether there was an additional reduction in clearance related to age in infants 1 to 4 months or simply inherent variability due to the low number of subjects studied in this age group. Since patients less than 6 months of age will only receive a single dose in PONV a decreased clearance is not likely to be clinically relevant.

- **Elderly**

  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 to 60 mL/min), both systemic clearance and volume of distribution are reduced following IV administration of ondansetron, resulting in a slight, but clinically insignificant, increase in elimination half-life (5.4 hours). A study in patients with severe renal impairment who required regular haemodialysis (studied between dialyses) showed ondansetron's pharmacokinetics to be essentially unchanged following IV administration.

- **Hepatic Impairment**

  In patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced with prolonged elimination half-lives (15 to 32 hours) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism.

**Pre Clinical 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 at clinically relevant concentrations. Dose-dependent QT prolongation has been observed in a thorough QT study in human volunteers (see Pharmacodynamic Effects – QT prolongation).

**INDICATIONS**

**Adults**

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

**Paediatric Population**

**Injection and oral formulations:**

ZOFRAN is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy. No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of post-operative nausea and vomiting; IV injection is recommended for this purpose.

**DOSE AND ADMINISTRATION**

Ondansetron (Zofran®) is available for oral and parenteral use to allow the route of administration and dosing to be flexible.

**CHEMOTHERAPY AND RADIOTHERAPY INDUCED NAUSEA AND VOMITING (CINV and RINV)**

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.

**Populations**

- **CINV and RINV in Adults**

  The recommended intravenous (IV) or intramuscular (IM) dose of Ondansetron (Zofran®) 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.

  The efficacy of Ondansetron (Zofran®) 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). Ondansetron (Zofran®) 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 Ondansetron (Zofran®) 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 6 months to 17 years)**

  The dose for CINV can be calculated based on body surface area (BSA) or weight. In paediatric clinical studies, Ondansetron (Zofran®) was given by IV infusion diluted in 25 to 50 mL of saline or other compatible infusion fluid (see Instructions for Use and Handling) and infused over not less than 15 minutes.
Dosing by BSA
Ondansetron (Zofran®) should be administered immediately before chemotherapy as a single IV dose of 5 mg/m². The IV dose must not exceed 8 mg. Oral dosing can commence 12 hours later and may be continued for up to 5 days (Table 1). Adult doses must not be exceeded.

Table 1. BSA-based dosing for CINV (aged 6 months to 17 years)

<table>
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<tr>
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<td>≥ 0.6 m² to ≤ 1.2 m²</td>
<td>5 mg/m² IV plus 4 mg syrup or tablet after 12 hours</td>
<td>4 mg syrup or tablet every 12 hours</td>
</tr>
<tr>
<td>&gt; 1.2 m²</td>
<td>5 mg/m² IV or 8 mg IV plus 8 mg syrup or tablet after 12 hours</td>
<td>8 mg syrup or tablet every 12 hours</td>
</tr>
</tbody>
</table>

Dosing by bodyweight
Ondansetron (Zofran®) should be administered immediately before chemotherapy as a single IV dose of 0.15 mg/kg. The IV dose must not exceed 8 mg. On Day 1, two further IV doses may be given in 4-hourly intervals. Oral dosing can commence 12 hours later and may be continued for up to 5 days (Table 2). Adult doses must not be exceeded.

Table 2. Weight-based dosing for CINV (aged 6 months to 17 years)

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Day 1</th>
<th>Days 2 - 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10 kg</td>
<td>Up to 3 doses of 0.15 mg/kg IV every 4 hours</td>
<td>2 mg syrup every 12 hours</td>
</tr>
<tr>
<td>&gt; 10 kg</td>
<td>Up to 3 doses of 0.15 mg/kg IV every 4 hours</td>
<td>4 mg syrup or tablet every 12 hours</td>
</tr>
</tbody>
</table>

- **CINV and RINV in Elderly**
  In patients 65 years of age or older, all IV 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 IV dose of Ondansetron (Zofran®) 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 IV dose of Ondansetron (Zofran®) 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)
- **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 and therefore.
  - **Patients with Poor Sparaine/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)**
- **PONV in Adults**
  For prevention of post-operative nausea and vomiting, the recommended dose of Ondansetron (Zofran®) 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 1 month to 17 years)**
  For prevention and treatment of PONV in paediatric patients having surgery performed under general anaesthesia, Ondansetron (Zofran®) 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.
- **Elderly**
  There is limited experience in the use of Ondansetron (Zofran®) in the prevention and treatment of post-operative nausea and vomiting in the elderly, however Ondansetron (Zofran®) 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 Sparaine/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.
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 preparation.

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

Ondansetron prolongs the QT interval in a dose-dependent manner (see Pharmacodynamic Effects). 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 (Zofran®) should be administered with caution to patients who have or may develop prolongation of QTc, including patients with electrolyte abnormalities, congestive heart failure, bradycardia, 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 Ondansetron (Zofran®) and other serotonergic drugs (see Interactions). If concomitant treatment with Ondansetron (Zofran®) 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.

Effects on Ability to Drive and Use Machines
In psychomotor testing Ondansetron (Zofran®) does not impair performance nor cause sedation. No detrimental effects on such activities are predicted from the pharmacology of Ondansetron (Zofran®).

DRUG INTERACTIONS
There is no evidence that Ondansetron (Zofran®) 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 (Zofran®) is administered with alcohol, temazepam, furosemide, 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.

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

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
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.

Serotonergic Drugs (e.g., SSRIs and SNRIs)
Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been described following the concomitant use of Ondansetron (Zofran®) and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs) (see Warnings and Precautions).

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

PREGNANCY AND LACTATION
Pregnancy
The safety of Ondansetron (Zofran®) 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 (Zofran®) 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 (Zofran®) should not breast-feed their babies.

ADVERSE EFFECTS
Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000) and very rare (<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 (Zofran®). The adverse event profiles in children and adolescents were comparable to that seen in adults.

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 dystonic reactions, oculogyric crisis and dyskinesia) have been observed without definitive evidence of persistent clinical sequelae.
Rare: Dizziness predominantly during rapid IV administration.

Eye disorders
Rare: Transient visual disturbances (eg. blurred vision) predominantly during IV 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.
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

Hepatobiliary disorders
Uncommon: Asymptomatic increases in liver function tests.
*These events were observed commonly 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 IV injection site reactions.

OVERDOSAGE AND TREATMENT
Symptoms and Signs
There is limited experience of Ondansetron (Zofran®) overdose. In the majority of cases symptoms were similar to those already reported in patients receiving recommended doses (see Adverse Effects).
Ondansetron prolongs QT interval in a dose-dependent fashion. ECG monitoring is recommended in cases of overdose.

Treatment
There is no specific antidote for Ondansetron (Zofran®), therefore in cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.
The use of ipecacuanha to treat overdose with Ondansetron (Zofran®) is not recommended as patients are unlikely to respond due to the anti-emetic action of ondansetron itself.

STORAGE CONDITION
Store at temperatures not exceeding 30°C. Protect from light.

COMPATIBILITY AND STABILITY
Incompatibilities
Ondansetron (Zofran®) injection should not be administered in the same syringe or infusion as any other medication (see Instructions for Use and Handling).
Ondansetron (Zofran®) injection should only be mixed with those infusion solutions which are recommended (see Instructions for Use and Handling).

INSTRUCTIONS FOR USE / HANDLING
Injection (unpreserved) ampoules:
The solution for injection formulation is unpreserved, should only be used once and injected or diluted immediately after opening. Any remaining solution should be discarded.
Ondansetron (Zofran®) injection ampoules should not be autoclaved.
Compatibility studies have been carried out in polyvinyl chloride infusion bags and polyvinyl chloride administration sets. Stability is 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 dextrose 5%w/v have been demonstrated to be stable in polypropylene syringes. Therefore, it is considered that unpreserved ondansetron injection diluted with compatible infusion fluids recommended below would also be stable in polypropylene syringes.
In keeping with good pharmaceutical practice, IV solutions should be prepared at the time of infusion, under appropriate aseptic conditions.
Compatibility with IV fluids
Compatibility studies have shown that unpreserved ondansetron injection is stable for seven days at room temperature (below 25°C) under fluorescent lighting or in a refrigerator with the following IV infusion fluids:
- Sodium Chloride IV Infusion BP 0.9%w/v.
- Glucose IV Infusion BP 5%w/v.
- Mannitol IV Infusion BP 10%w/v.
- Ringers IV Infusion.
- Potassium Chloride 0.3%w/v and Sodium Chloride 0.9%w/v IV Infusion BP.
- Potassium Chloride 0.3%w/v and Glucose 5%w/v IV Infusion BP.
Compatibility with other drugs
Ondansetron (Zofran®) may be administered by IV infusion at 1 mg/h, 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 160 micrograms/mL (e.g. 8 mg/500mL and 8 mg/50mL respectively):

<table>
<thead>
<tr>
<th>Drug</th>
<th>Compatibility Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cisplatin</strong></td>
<td>Concentrations up to 0.48 mg/mL (e.g. 240 mg in 500 mL) administered over one to eight hours.</td>
</tr>
<tr>
<td><strong>5-fluorouracil</strong></td>
<td>Concentrations up to 0.8 mg/mL (e.g. 2.4 g in 3 litres or 400 mg in 500 mL) administered at a rate of at least 20 mL/h (500 mL 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.</td>
</tr>
<tr>
<td><strong>Carboplatin</strong></td>
<td>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 10 minutes to 1 hour.</td>
</tr>
<tr>
<td><strong>Etoposide</strong></td>
<td>Concentrations in the range 0.144 mg/mL to 0.25 mg/mL (e.g., 72 mg in 500 mL to 250 mg in 1L), administered over 30 minutes to 1 hour.</td>
</tr>
<tr>
<td><strong>Ceftazidime</strong></td>
<td>Doses in the range 250 mg to 2000 mg reconstituted with Water for Injections BP as recommended by the manufacturer (e.g. 2.5mL for 250 mg and 10mL for 2 g ceftazidime) and given as an IV bolus injection over approximately 5 minutes.</td>
</tr>
<tr>
<td><strong>Cyclophosphamide</strong></td>
<td>Doses in the range 100 mg to 1 g, reconstituted with Water for Injections BP, 5 mL per 100 mg cyclophosphamide, as recommended by the manufacturer, and given as an IV bolus injection over approximately 5 minutes.</td>
</tr>
<tr>
<td><strong>Doxorubicin</strong></td>
<td>Doses in the range 10 to 100 mg reconstituted with Water for Injections BP, 5 mL per 10 mg doxorubicin, as recommended by the manufacturer and given as an IV bolus injection over approximately five minutes.</td>
</tr>
<tr>
<td><strong>Dexamethasone</strong></td>
<td>Dexamethasone sodium phosphate 20 mg may be administered as a slow IV injection over 2 to 5 minutes via the Y-site of an infusion set delivering 8 to 16 mg of ondansetron diluted in 50 to 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 micrograms to 2.5 mg/mL for dexamethasone sodium phosphate and 8 micrograms to 1 mg/mL for ondansetron.</td>
</tr>
</tbody>
</table>

**AVAILABILITY**
Ondansetron (Zofran®) 4mg / 2mL Solution for Injection: Box of 5 ampoules
Ondansetron (Zofran®) 8mg / 4mL Solution for Injection: Box of 5 ampoules

**CAUTION**
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
Keep all medicines out of reach of children.

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Version Number: GDS38/IP114 Revision Date: 3 April 2014

Imported by:
GlaxoSmithKline Philippines Inc
2266 Chino Roces Avenue, City of Makati
Tel: 892-07-61

Manufactured by:
GlaxoSmithKline Manufacturing S.p.A.
Parma, Italy