

## Zofran Injection 2mg/ml - PL00004/0375

### Annex - Revised wording to SPC and Technical Leaflet of Patient Information Leaflet (PIL)

Present	Revised
<p>SPC: Section 4.2 Posology &amp; Method of Administration</p> <p>A single dose of 32mg diluted in 50-100ml of saline or other compatible infusion fluid (see <i>Pharmaceutical Precautions</i>) and infused over not less than 15 minutes immediately before chemotherapy.</p>	<p>SPC: Section 4.2 Posology &amp; Method of Administration</p> <p>A single <u>intravenous</u> dose of <u>16mg</u> diluted in 50-100ml of saline or other compatible infusion fluid (see <i>Pharmaceutical Precautions</i>) and infused over not less than 15 minutes immediately before chemotherapy. <u>A single dose greater than 16 mg must not be given due to dose dependent increase of QT-prolongation risk (see sections 4.4, 4.8 and 5.1)</u></p>
<p>SPC: Section 5.1 Pharmacodynamic Properties</p> <p>Ondansetron is a potent, highly selective 5HT<sub>3</sub> 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 5HT<sub>3</sub> 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 5HT<sub>3</sub> 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.</p> <p>Ondansetron does not alter plasma prolactin concentrations.</p> <p>The role of ondansetron in opiate-induced emesis is not yet established.</p>	<p>SPC: Section 5.1 Pharmacodynamic Properties</p> <p>Ondansetron is a potent, highly selective 5HT<sub>3</sub> 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 5HT<sub>3</sub> 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 5HT<sub>3</sub> 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.</p> <p>Ondansetron does not alter plasma prolactin concentrations.</p> <p>The role of ondansetron in opiate-induced emesis is not yet established.</p> <p><u>The effect of ondansetron on the QTc interval was evaluated in a double blind, randomised, 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)</u></p>

	<p><u>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. No significant changes were seen in the measured electrocardiographic PR or QRS intervals.</u></p>
<p>SPC:  <b>6.6. Instruction for Use/Handling</b>  <i>Dexamethasone:</i> 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 32mg of ondansetron diluted in 50-100ml 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 - 2.5mg/ml for dexamethasone sodium phosphate and 8 microgram - 1mg/ml for ondansetron.</p>	<p>SPC:  <b>6.6. Instruction for Use/Handling</b>  <i>Dexamethasone:</i> 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 <u>16mg</u> of ondansetron diluted in 50-100ml 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 - 2.5mg/ml for dexamethasone sodium phosphate and 8 microgram - 1mg/ml for ondansetron.</p>
<p>Technical Leaflet of PIL:  Posology &amp; Method of Administration</p> <p>Chemotherapy and Radiotherapy  Adults  <i>Highly emetogenic chemotherapy:</i>  For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, Zofran can be given either by rectal, intravenous or intramuscular administration. Zofran has been shown to be equally effective in the following dose schedules over the first 24 hours of chemotherapy:</p> <ul style="list-style-type: none"> <li>• A single dose of 8mg by slow intravenous or intramuscular injection immediately before chemotherapy.</li> <li>• A dose of 8mg by slow intravenous or intramuscular injection immediately before chemotherapy, followed by two further intravenous or intramuscular doses of 8mg two to four hours apart, or by a constant infusion of 1mg/hour for up to 24 hours.</li> <li>• A single dose of 32mg diluted in 50-100ml of saline or other compatible infusion fluid (See Instructions for Use/Handling) and infused over not less than 15 minutes immediately before chemotherapy.</li> </ul> <p>The selection of dose regimen should be determined by the severity of the emetogenic challenge.</p>	<p>Technical Leaflet of PIL:  Posology &amp; Method of Administration</p> <p>Chemotherapy and Radiotherapy  Adults  <i>Highly emetogenic chemotherapy:</i>  For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, Zofran can be given either by rectal, intravenous or intramuscular administration. Zofran has been shown to be equally effective in the following dose schedules over the first 24 hours of chemotherapy:</p> <ul style="list-style-type: none"> <li>• A single dose of 8mg by slow intravenous or intramuscular injection immediately before chemotherapy.</li> <li>• A dose of 8mg by slow intravenous or intramuscular injection immediately before chemotherapy, followed by two further intravenous or intramuscular doses of 8mg two to four hours apart, or by a constant infusion of 1mg/hour for up to 24 hours.</li> <li>• A single dose of <u>16mg</u> diluted in 50-100ml of saline or other compatible infusion fluid (See Instructions for Use/Handling) and infused over not less than 15 minutes immediately before chemotherapy.</li> </ul> <p>The selection of dose regimen should be determined by the severity of the emetogenic challenge.</p> <p><u>A single dose greater than 16 mg must not be given due to dose dependent increase of QT-prolongation risk (see sections 4.4, 4.8 and</u></p>

	<u>5.1 of the SPC)</u>
<p>Technical Leaflet of PIL:</p> <p>Instructions for Use/Handling</p> <p>Compatibility with other drugs  <i>Dexamethasone</i>: 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 32mg of ondansetron diluted in 50-100ml 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 - 2.5mg/ml for dexamethasone sodium phosphate and 8 microgram - 1mg/ml for ondansetron.</p>	<p>Technical Leaflet of PIL:</p> <p>Instructions for Use/Handling</p> <p>Compatibility with other drugs  <i>Dexamethasone</i>: 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 <u>16mg</u> of ondansetron diluted in 50-100ml 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 - 2.5mg/ml for dexamethasone sodium phosphate and 8 microgram - 1mg/ml for ondansetron.</p>