

PRESCRIBING INFORMATION

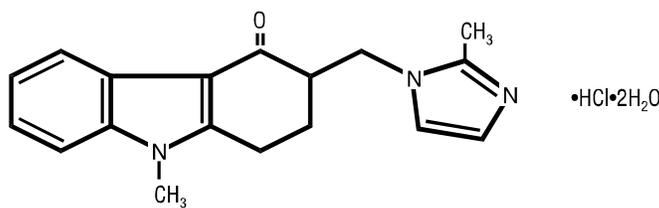
**ZOFRAN<sup>®</sup>**  
**(ondansetron hydrochloride)**  
**Tablets**

**ZOFRAN ODT<sup>®</sup>**  
**(ondansetron)**  
**Orally Disintegrating Tablets**

**ZOFRAN<sup>®</sup>**  
**(ondansetron hydrochloride)**  
**Oral Solution**

**DESCRIPTION**

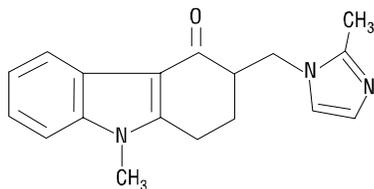
The active ingredient in ZOFRAN Tablets and ZOFRAN Oral Solution is ondansetron hydrochloride (HCl) as the dihydrate, the racemic form of ondansetron and a selective blocking agent of the serotonin 5-HT<sub>3</sub> receptor type. Chemically it is (±) 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, monohydrochloride, dihydrate. It has the following structural formula:



The empirical formula is C<sub>18</sub>H<sub>19</sub>N<sub>3</sub>O·HCl·2H<sub>2</sub>O, representing a molecular weight of 365.9.

Ondansetron HCl dihydrate is a white to off-white powder that is soluble in water and normal saline.

The active ingredient in ZOFRAN ODT Orally Disintegrating Tablets is ondansetron base, the racemic form of ondansetron, and a selective blocking agent of the serotonin 5-HT<sub>3</sub> receptor type. Chemically it is (±) 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one. It has the following structural formula:



31 The empirical formula is  $C_{18}H_{19}N_3O$  representing a molecular weight of 293.4.

32 Each 4-mg ZOFRAN Tablet for oral administration contains ondansetron HCl dihydrate  
33 equivalent to 4 mg of ondansetron. Each 8-mg ZOFRAN Tablet for oral administration contains  
34 ondansetron HCl dihydrate equivalent to 8 mg of ondansetron. Each 24-mg ZOFRAN Tablet for  
35 oral administration contains ondansetron HCl dihydrate equivalent to 24 mg of ondansetron. Each  
36 tablet also contains the inactive ingredients lactose, microcrystalline cellulose, pregelatinized  
37 starch, hypromellose, magnesium stearate, titanium dioxide, triacetin, iron oxide yellow (8-mg  
38 tablet only), and iron oxide red (24-mg tablet only).

39 Each 4-mg ZOFRAN ODT Orally Disintegrating Tablet for oral administration contains 4 mg  
40 ondansetron base. Each 8-mg ZOFRAN ODT Orally Disintegrating Tablet for oral administration  
41 contains 8 mg ondansetron base. Each ZOFRAN ODT Tablet also contains the inactive  
42 ingredients aspartame, gelatin, mannitol, methylparaben sodium, propylparaben sodium, and  
43 strawberry flavor. ZOFRAN ODT Tablets are a freeze-dried, orally administered formulation of  
44 ondansetron which rapidly disintegrates on the tongue and does not require water to aid  
45 dissolution or swallowing.

46 Each 5 mL of ZOFRAN Oral Solution contains 5 mg of ondansetron HCl dihydrate equivalent  
47 to 4 mg of ondansetron. ZOFRAN Oral Solution contains the inactive ingredients citric acid  
48 anhydrous, purified water, sodium benzoate, sodium citrate, sorbitol, and strawberry flavor.

## 49 **CLINICAL PHARMACOLOGY**

50 **Pharmacodynamics:** Ondansetron is a selective 5-HT<sub>3</sub> receptor antagonist. While its  
51 mechanism of action has not been fully characterized, ondansetron is not a dopamine-receptor  
52 antagonist. Serotonin receptors of the 5-HT<sub>3</sub> type are present both peripherally on vagal nerve  
53 terminals and centrally in the chemoreceptor trigger zone of the area postrema. It is not certain  
54 whether ondansetron's antiemetic action is mediated centrally, peripherally, or in both sites.  
55 However, cytotoxic chemotherapy appears to be associated with release of serotonin from the  
56 enterochromaffin cells of the small intestine. In humans, urinary 5-HIAA (5-hydroxyindoleacetic  
57 acid) excretion increases after cisplatin administration in parallel with the onset of emesis. The  
58 released serotonin may stimulate the vagal afferents through the 5-HT<sub>3</sub> receptors and initiate the  
59 vomiting reflex.

60 In animals, the emetic response to cisplatin can be prevented by pretreatment with an inhibitor  
61 of serotonin synthesis, bilateral abdominal vagotomy and greater splanchnic nerve section, or  
62 pretreatment with a serotonin 5-HT<sub>3</sub> receptor antagonist.

63 In normal volunteers, single intravenous doses of 0.15 mg/kg of ondansetron had no effect on  
64 esophageal motility, gastric motility, lower esophageal sphincter pressure, or small intestinal  
65 transit time. Multiday administration of ondansetron has been shown to slow colonic transit in  
66 normal volunteers. Ondansetron has no effect on plasma prolactin concentrations.

67 Ondansetron does not alter the respiratory depressant effects produced by alfentanil or the  
68 degree of neuromuscular blockade produced by atracurium. Interactions with general or local  
69 anesthetics have not been studied.

70 **Pharmacokinetics:** Ondansetron is well absorbed from the gastrointestinal tract and undergoes  
71 some first-pass metabolism. Mean bioavailability in healthy subjects, following administration of  
72 a single 8-mg tablet, is approximately 56%.

73 Ondansetron systemic exposure does not increase proportionately to dose. AUC from a 16-mg  
74 tablet was 24% greater than predicted from an 8-mg tablet dose. This may reflect some reduction  
75 of first-pass metabolism at higher oral doses. Bioavailability is also slightly enhanced by the  
76 presence of food but unaffected by antacids.

77 Ondansetron is extensively metabolized in humans, with approximately 5% of a radiolabeled  
78 dose recovered from the urine as the parent compound. The primary metabolic pathway is  
79 hydroxylation on the indole ring followed by subsequent glucuronide or sulfate conjugation.  
80 Although some nonconjugated metabolites have pharmacologic activity, these are not found in  
81 plasma at concentrations likely to significantly contribute to the biological activity of ondansetron.

82 In vitro metabolism studies have shown that ondansetron is a substrate for human hepatic  
83 cytochrome P-450 enzymes, including CYP1A2, CYP2D6, and CYP3A4. In terms of overall  
84 ondansetron turnover, CYP3A4 played the predominant role. Because of the multiplicity of  
85 metabolic enzymes capable of metabolizing ondansetron, it is likely that inhibition or loss of one  
86 enzyme (e.g., CYP2D6 genetic deficiency) will be compensated by others and may result in little  
87 change in overall rates of ondansetron elimination. Ondansetron elimination may be affected by  
88 cytochrome P-450 inducers. In a pharmacokinetic study of 16 epileptic patients maintained  
89 chronically on CYP3A4 inducers, carbamazepine, or phenytoin, reduction in AUC,  $C_{max}$ , and  $T_{1/2}$   
90 of ondansetron was observed.<sup>1</sup> This resulted in a significant increase in clearance. However, on  
91 the basis of available data, no dosage adjustment for ondansetron is recommended (see  
92 PRECAUTIONS: [Drug Interactions](#)).

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

95 Gender differences were shown in the disposition of ondansetron given as a single dose. The  
96 extent and rate of ondansetron's absorption is greater in women than men. Slower clearance in  
97 women, a smaller apparent volume of distribution (adjusted for weight), and higher absolute  
98 bioavailability resulted in higher plasma ondansetron levels. These higher plasma levels may in  
99 part be explained by differences in body weight between men and women. It is not known whether  
100 these gender-related differences were clinically important. More detailed pharmacokinetic  
101 information is contained in [Tables 1](#) and [2](#) taken from 2 studies.

102

103 **Table 1. Pharmacokinetics in Normal Volunteers: Single 8-mg ZOFTRAN Tablet Dose**

Age-group (years)	Mean Weight (kg)	n	Peak Plasma Concentration (ng/mL)	Time of Peak Plasma Concentration (h)	Mean Elimination Half-life (h)	Systemic Plasma Clearance L/h/kg	Absolute Bioavailability
18-40 M	69.0	6	26.2	2.0	3.1	0.403	0.483
F	62.7	5	42.7	1.7	3.5	0.354	0.663
61-74 M	77.5	6	24.1	2.1	4.1	0.384	0.585
F	60.2	6	52.4	1.9	4.9	0.255	0.643
≥75 M	78.0	5	37.0	2.2	4.5	0.277	0.619
F	67.6	6	46.1	2.1	6.2	0.249	0.747

104

105 **Table 2. Pharmacokinetics in Normal Volunteers: Single 24-mg ZOFTRAN Tablet Dose**

Age-group (years)	Mean Weight (kg)	n	Peak Plasma Concentration (ng/mL)	Time of Peak Plasma Concentration (h)	Mean Elimination Half-life (h)
18-43 M	84.1	8	125.8	1.9	4.7
F	71.8	8	194.4	1.6	5.8

106

107 A reduction in clearance and increase in elimination half-life are seen in patients over 75 years  
108 of age. In clinical trials with cancer patients, safety and efficacy was similar in patients over  
109 65 years of age and those under 65 years of age; there was an insufficient number of patients over  
110 75 years of age to permit conclusions in that age-group. No dosage adjustment is recommended  
111 in the elderly.

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

117 Due to the very small contribution (5%) of renal clearance to the overall clearance, renal  
118 impairment was not expected to significantly influence the total clearance of ondansetron.  
119 However, ondansetron oral mean plasma clearance was reduced by about 50% in patients with  
120 severe renal impairment (creatinine clearance <30 mL/min). This reduction in clearance is  
121 variable and was not consistent with an increase in half-life. No reduction in dose or dosing  
122 frequency in these patients is warranted.

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

125 Four- and 8-mg doses of either ZOFTRAN Oral Solution or ZOFTRAN ODT Orally  
126 Disintegrating Tablets are bioequivalent to corresponding doses of ZOFTRAN Tablets and may be  
127 used interchangeably. One 24-mg ZOFTRAN Tablet is bioequivalent to and interchangeable with  
128 three 8-mg ZOFTRAN Tablets.

## 129 **CLINICAL TRIALS**

### 130 **Chemotherapy-Induced Nausea and Vomiting: *Highly Emetogenic Chemotherapy:***

131 In 2 randomized, double-blind, monotherapy trials, a single 24-mg ZOFTRAN Tablet was  
132 superior to a relevant historical placebo control in the prevention of nausea and vomiting  
133 associated with highly emetogenic cancer chemotherapy, including cisplatin  $\geq 50$  mg/m<sup>2</sup>. Steroid  
134 administration was excluded from these clinical trials. More than 90% of patients receiving a  
135 cisplatin dose  $\geq 50$  mg/m<sup>2</sup> in the historical placebo comparator experienced vomiting in the absence  
136 of antiemetic therapy.

137 The first trial compared oral doses of ondansetron 24 mg once a day, 8 mg twice a day, and  
138 32 mg once a day in 357 adult cancer patients receiving chemotherapy regimens containing  
139 cisplatin  $\geq 50$  mg/m<sup>2</sup>. A total of 66% of patients in the ondansetron 24-mg once a day group, 55%  
140 in the ondansetron 8-mg twice a day group, and 55% in the ondansetron 32-mg once a day group  
141 completed the 24-hour study period with 0 emetic episodes and no rescue antiemetic medications,  
142 the primary endpoint of efficacy. Each of the 3 treatment groups was shown to be statistically  
143 significantly superior to a historical placebo control.

144 In the same trial, 56% of patients receiving oral ondansetron 24 mg once a day experienced no  
145 nausea during the 24-hour study period, compared with 36% of patients in the oral ondansetron  
146 8-mg twice a day group ( $p = 0.001$ ) and 50% in the oral ondansetron 32-mg once a day group.

147 In a second trial, efficacy of the oral ondansetron 24 mg once a day regimen in the prevention  
148 of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including  
149 cisplatin  $\geq 50$  mg/m<sup>2</sup>, was confirmed.

150 ***Moderately Emetogenic Chemotherapy:*** In 1 double-blind US study in 67 patients,  
151 ZOFTRAN Tablets 8 mg administered twice a day were significantly more effective than placebo  
152 in preventing vomiting induced by cyclophosphamide-based chemotherapy containing  
153 doxorubicin. Treatment response is based on the total number of emetic episodes over the 3-day  
154 study period. The results of this study are summarized in [Table 3:](#)

155

156 **Table 3. Emetic Episodes: Treatment Response**

	Ondansetron 8-mg b.i.d. ZOFTRAN Tablets*	Placebo	p Value
Number of patients	33	34	
Treatment response			
0 Emetic episodes	20 (61%)	2 (6%)	<0.001
1-2 Emetic episodes	6 (18%)	8 (24%)	
More than 2 emetic episodes/withdrawn	7 (21%)	24 (71%)	<0.001
Median number of emetic episodes	0.0	Undefined <sup>†</sup>	
Median time to first emetic episode (h)	Undefined <sup>‡</sup>	6.5	

157 \* The first dose was administered 30 minutes before the start of emetogenic chemotherapy, with  
158 a subsequent dose 8 hours after the first dose. An 8-mg ZOFTRAN Tablet was administered  
159 twice a day for 2 days after completion of chemotherapy.

160 <sup>†</sup> Median undefined since at least 50% of the patients were withdrawn or had more than 2 emetic  
161 episodes.

162 <sup>‡</sup> Median undefined since at least 50% of patients did not have any emetic episodes.

163

164 In 1 double-blind US study in 336 patients, ZOFTRAN Tablets 8 mg administered twice a day  
165 were as effective as ZOFTRAN Tablets 8 mg administered 3 times a day in preventing nausea and  
166 vomiting induced by cyclophosphamide-based chemotherapy containing either methotrexate or  
167 doxorubicin. Treatment response is based on the total number of emetic episodes over the 3-day  
168 study period. The results of this study are summarized in [Table 4](#):

169

170 **Table 4. Emetic Episodes: Treatment Response**

	Ondansetron	
	8-mg b.i.d. ZOFTRAN Tablets*	8-mg t.i.d. ZOFTRAN Tablets <sup>†</sup>
Number of patients	165	171
Treatment response		
0 Emetic episodes	101 (61%)	99 (58%)
1-2 Emetic episodes	16 (10%)	17 (10%)
More than 2 emetic episodes/withdrawn	48 (29%)	55 (32%)
Median number of emetic episodes	0.0	0.0
Median time to first emetic episode (h)	Undefined <sup>‡</sup>	Undefined <sup>‡</sup>
Median nausea scores (0-100) <sup>§</sup>	6	6

171 \* The first dose was administered 30 minutes before the start of emetogenic chemotherapy, with  
172 a subsequent dose 8 hours after the first dose. An 8-mg ZOFTRAN Tablet was administered  
173 twice a day for 2 days after completion of chemotherapy.

174 † The first dose was administered 30 minutes before the start of emetogenic chemotherapy, with  
175 subsequent doses 4 and 8 hours after the first dose. An 8-mg ZOFTRAN Tablet was  
176 administered 3 times a day for 2 days after completion of chemotherapy.

177 ‡ Median undefined since at least 50% of patients did not have any emetic episodes.

178 § Visual analog scale assessment: 0 = no nausea, 100 = nausea as bad as it can be.

179

180 **Re-treatment:** In uncontrolled trials, 148 patients receiving cyclophosphamide-based  
181 chemotherapy were re-treated with ZOFTRAN Tablets 8 mg 3 times daily of oral ondansetron  
182 during subsequent chemotherapy for a total of 396 re-treatment courses. No emetic episodes  
183 occurred in 314 (79%) of the re-treatment courses, and only 1 to 2 emetic episodes occurred in 43  
184 (11%) of the re-treatment courses.

185 **Pediatric Studies:** Three open-label, uncontrolled, foreign trials have been performed with  
186 182 pediatric patients 4 to 18 years old with cancer who were given a variety of cisplatin or  
187 noncisplatin regimens. In these foreign trials, the initial dose of ZOFTRAN<sup>®</sup> (ondansetron HCl)  
188 Injection ranged from 0.04 to 0.87 mg/kg for a total dose of 2.16 to 12 mg. This was followed by  
189 the administration of ZOFTRAN Tablets ranging from 4 to 24 mg daily for 3 days. In these studies,  
190 58% of the 170 evaluable patients had a complete response (no emetic episodes) on day 1. Two  
191 studies showed the response rates for patients less than 12 years of age who received ZOFTRAN  
192 Tablets 4 mg 3 times a day to be similar to those in patients 12 to 18 years of age who received  
193 ZOFTRAN Tablets 8 mg 3 times daily. Thus, prevention of emesis in these pediatric patients was  
194 essentially the same as for patients older than 18 years of age. Overall, ZOFTRAN Tablets were  
195 well tolerated in these pediatric patients.

196 **Radiation-Induced Nausea and Vomiting: Total Body Irradiation:** In a randomized,  
197 double-blind study in 20 patients, ZOFTRAN Tablets (8 mg given 1.5 hours before each fraction of  
198 radiotherapy for 4 days) were significantly more effective than placebo in preventing vomiting  
199 induced by total body irradiation. Total body irradiation consisted of 11 fractions (120 cGy per  
200 fraction) over 4 days for a total of 1,320 cGy. Patients received 3 fractions for 3 days, then  
201 2 fractions on day 4.

202 **Single High-Dose Fraction Radiotherapy:** Ondansetron was significantly more effective  
203 than metoclopramide with respect to complete control of emesis (0 emetic episodes) in a  
204 double-blind trial in 105 patients receiving single high-dose radiotherapy (800 to 1,000 cGy) over  
205 an anterior or posterior field size of  $\geq 80$  cm<sup>2</sup> to the abdomen. Patients received the first dose of  
206 ZOFTRAN Tablets (8 mg) or metoclopramide (10 mg) 1 to 2 hours before radiotherapy. If  
207 radiotherapy was given in the morning, 2 additional doses of study treatment were given (1 tablet  
208 late afternoon and 1 tablet before bedtime). If radiotherapy was given in the afternoon, patients  
209 took only 1 further tablet that day before bedtime. Patients continued the oral medication on a  
210 3 times a day basis for 3 days.

211 **Daily Fractionated Radiotherapy:** Ondansetron was significantly more effective than  
212 prochlorperazine with respect to complete control of emesis (0 emetic episodes) in a double-blind  
213 trial in 135 patients receiving a 1- to 4-week course of fractionated radiotherapy (180 cGy doses)  
214 over a field size of  $\geq 100$  cm<sup>2</sup> to the abdomen. Patients received the first dose of ZOFTRAN Tablets  
215 (8 mg) or prochlorperazine (10 mg) 1 to 2 hours before the patient received the first daily  
216 radiotherapy fraction, with 2 subsequent doses on a 3 times a day basis. Patients continued the oral  
217 medication on a 3 times a day basis on each day of radiotherapy.

218 **Postoperative Nausea and Vomiting:** Surgical patients who received ondansetron 1 hour  
219 before the induction of general balanced anesthesia (barbiturate: thiopental, methohexital, or  
220 thiamylal; opioid: alfentanil, sufentanil, morphine, or fentanyl; nitrous oxide; neuromuscular  
221 blockade: succinylcholine/curare or gallamine and/or vecuronium, pancuronium, or atracurium;  
222 and supplemental isoflurane or enflurane) were evaluated in 2 double-blind studies (1 US study,  
223 1 foreign) involving 865 patients. ZOFTRAN Tablets (16 mg) were significantly more effective  
224 than placebo in preventing postoperative nausea and vomiting.

225 The study populations in all trials thus far consisted of women undergoing inpatient surgical  
226 procedures. No studies have been performed in males. No controlled clinical study comparing  
227 ZOFTRAN Tablets to ZOFTRAN Injection has been performed.

## 228 **INDICATIONS AND USAGE**

- 229 1. Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy,  
230 including cisplatin  $\geq 50$  mg/m<sup>2</sup>.
- 231 2. Prevention of nausea and vomiting associated with initial and repeat courses of moderately  
232 emetogenic cancer chemotherapy.

- 233 3. Prevention of nausea and vomiting associated with radiotherapy in patients receiving either  
234 total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the  
235 abdomen.
- 236 4. Prevention of postoperative nausea and/or vomiting. As with other antiemetics, routine  
237 prophylaxis is not recommended for patients in whom there is little expectation that nausea  
238 and/or vomiting will occur postoperatively. In patients where nausea and/or vomiting must be  
239 avoided postoperatively, ZOFTRAN Tablets, ZOFTRAN ODT Orally Disintegrating Tablets,  
240 and ZOFTRAN Oral Solution are recommended even where the incidence of postoperative  
241 nausea and/or vomiting is low.

## 242 **CONTRAINDICATIONS**

243 ZOFTRAN Tablets, ZOFTRAN ODT Orally Disintegrating Tablets, and ZOFTRAN Oral Solution  
244 are contraindicated for patients known to have hypersensitivity to the drug.

## 245 **WARNINGS**

246 Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity  
247 to other selective 5-HT<sub>3</sub> receptor antagonists.

## 248 **PRECAUTIONS**

249 Ondansetron is not a drug that stimulates gastric or intestinal peristalsis. It should not be used  
250 instead of nasogastric suction. The use of ondansetron in patients following abdominal surgery or  
251 in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or  
252 gastric distension.

253 **Information for Patients: *Phenylketonurics*:** Phenylketonuric patients should be informed  
254 that ZOFTRAN ODT Orally Disintegrating Tablets contain phenylalanine (a component of  
255 aspartame). Each 4-mg and 8-mg orally disintegrating tablet contains <0.03 mg phenylalanine.

256 Patients should be instructed not to remove ZOFTRAN ODT Tablets from the blister until just  
257 prior to dosing. The tablet should not be pushed through the foil. With dry hands, the blister  
258 backing should be peeled completely off the blister. The tablet should be gently removed and  
259 immediately placed on the tongue to dissolve and be swallowed with the saliva. Peelable  
260 illustrated stickers are affixed to the product carton that can be provided with the prescription to  
261 ensure proper use and handling of the product.

262 **Drug Interactions:** Ondansetron does not itself appear to induce or inhibit the cytochrome  
263 P-450 drug-metabolizing enzyme system of the liver (see CLINICAL PHARMACOLOGY,  
264 [Pharmacokinetics](#)). Because ondansetron is metabolized by hepatic cytochrome P-450  
265 drug-metabolizing enzymes (CYP3A4, CYP2D6, CYP1A2), inducers or inhibitors of these  
266 enzymes may change the clearance and, hence, the half-life of ondansetron. On the basis of  
267 available data, no dosage adjustment is recommended for patients on these drugs.

268 ***Phenytoin, Carbamazepine, and Rifampicin*:** In patients treated with potent inducers of  
269 CYP3A4 (i.e., phenytoin, carbamazepine, and rifampicin), the clearance of ondansetron was  
270 significantly increased and ondansetron blood concentrations were decreased. However, on the

271 basis of available data, no dosage adjustment for ondansetron is recommended for patients on  
272 these drugs.<sup>1,3</sup>

273 **Tramadol:** Although no pharmacokinetic drug interaction between ondansetron and tramadol  
274 has been observed, data from 2 small studies indicate that ondansetron may be associated with an  
275 increase in patient controlled administration of tramadol.<sup>4,5</sup>

276 **Chemotherapy:** Tumor response to chemotherapy in the P-388 mouse leukemia model is not  
277 affected by ondansetron. In humans, carmustine, etoposide, and cisplatin do not affect the  
278 pharmacokinetics of ondansetron.

279 In a crossover study in 76 pediatric patients, I.V. ondansetron did not increase blood levels of  
280 high-dose methotrexate.

281 **Use in Surgical Patients:** The coadministration of ondansetron had no effect on the  
282 pharmacokinetics and pharmacodynamics of temazepam.

283 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenic effects were not  
284 seen in 2-year studies in rats and mice with oral ondansetron doses up to 10 and 30 mg/kg/day,  
285 respectively. Ondansetron was not mutagenic in standard tests for mutagenicity. Oral  
286 administration of ondansetron up to 15 mg/kg/day did not affect fertility or general reproductive  
287 performance of male and female rats.

288 **Pregnancy: Teratogenic Effects:** Pregnancy Category B. Reproduction studies have been  
289 performed in pregnant rats and rabbits at daily oral doses up to 15 and 30 mg/kg/day, respectively,  
290 and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There  
291 are, however, no adequate and well-controlled studies in pregnant women. Because animal  
292 reproduction studies are not always predictive of human response, this drug should be used during  
293 pregnancy only if clearly needed.

294 **Nursing Mothers:** Ondansetron is excreted in the breast milk of rats. It is not known whether  
295 ondansetron is excreted in human milk. Because many drugs are excreted in human milk, caution  
296 should be exercised when ondansetron is administered to a nursing woman.

297 **Pediatric Use:** Little information is available about dosage in pediatric patients 4 years of age or  
298 younger (see [CLINICAL PHARMACOLOGY](#) and [DOSAGE AND ADMINISTRATION](#)  
299 sections for use in pediatric patients 4 to 18 years of age).

300 **Geriatric Use:** Of the total number of subjects enrolled in cancer chemotherapy-induced and  
301 postoperative nausea and vomiting in US- and foreign-controlled clinical trials, for which there  
302 were subgroup analyses, 938 were 65 years of age and over. No overall differences in safety or  
303 effectiveness were observed between these subjects and younger subjects, and other reported  
304 clinical experience has not identified differences in responses between the elderly and younger  
305 patients, but greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment  
306 is not needed in patients over the age of 65 (see [CLINICAL PHARMACOLOGY](#)).

307 **ADVERSE REACTIONS**

308 The following have been reported as adverse events in clinical trials of patients treated with  
309 ondansetron, the active ingredient of ZOFRAN. A causal relationship to therapy with ZOFRAN  
310 has been unclear in many cases.

311 **Chemotherapy-Induced Nausea and Vomiting:** The adverse events in Table 5 have been  
312 reported in  $\geq 5\%$  of adult patients receiving a single 24-mg ZOFRAN Tablet in 2 trials. These  
313 patients were receiving concurrent highly emetogenic cisplatin-based chemotherapy regimens  
314 (cisplatin dose  $\geq 50$  mg/m<sup>2</sup>).

315

316 **Table 5. Principal Adverse Events in US Trials: Single Day Therapy With 24-mg ZOFRAN**  
317 **Tablets (Highly Emetogenic Chemotherapy)**

Event	Ondansetron 24 mg q.d. n = 300	Ondansetron 8 mg b.i.d. n = 124	Ondansetron 32 mg q.d. n = 117
Headache	33 (11%)	16 (13%)	17 (15%)
Diarrhea	13 (4%)	9 (7%)	3 (3%)

318

319 The adverse events in Table 6 have been reported in  $\geq 5\%$  of adults receiving either 8 mg of  
320 ZOFRAN Tablets 2 or 3 times a day for 3 days or placebo in 4 trials. These patients were  
321 receiving concurrent moderately emetogenic chemotherapy, primarily cyclophosphamide-based  
322 regimens.

323

324 **Table 6. Principal Adverse Events in US Trials: 3 Days of Therapy With 8-mg ZOFRAN**  
325 **Tablets (Moderately Emetogenic Chemotherapy)**

Event	Ondansetron 8 mg b.i.d. n = 242	Ondansetron 8 mg t.i.d. n = 415	Placebo n = 262
Headache	58 (24%)	113 (27%)	34 (13%)
Malaise/fatigue	32 (13%)	37 (9%)	6 (2%)
Constipation	22 (9%)	26 (6%)	1 (<1%)
Diarrhea	15 (6%)	16 (4%)	10 (4%)
Dizziness	13 (5%)	18 (4%)	12 (5%)

326

327 **Central Nervous System:** There have been rare reports consistent with, but not diagnostic  
328 of, extrapyramidal reactions in patients receiving ondansetron.

329 **Hepatic:** In 723 patients receiving cyclophosphamide-based chemotherapy in US clinical  
330 trials, AST and/or ALT values have been reported to exceed twice the upper limit of normal in  
331 approximately 1% to 2% of patients receiving ZOFRAN Tablets. The increases were transient and  
332 did not appear to be related to dose or duration of therapy. On repeat exposure, similar transient  
333 elevations in transaminase values occurred in some courses, but symptomatic hepatic disease did

334 not occur. The role of cancer chemotherapy in these biochemical changes cannot be clearly  
335 determined.

336 There have been reports of liver failure and death in patients with cancer receiving concurrent  
337 medications including potentially hepatotoxic cytotoxic chemotherapy and antibiotics. The  
338 etiology of the liver failure is unclear.

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

340 **Other:** Rare cases of anaphylaxis, bronchospasm, tachycardia, angina (chest pain),  
341 hypokalemia, electrocardiographic alterations, vascular occlusive events, and grand mal seizures  
342 have been reported. Except for bronchospasm and anaphylaxis, the relationship to ZOFTRAN was  
343 unclear.

344 **Radiation-Induced Nausea and Vomiting:** The adverse events reported in patients receiving  
345 ZOFTRAN Tablets and concurrent radiotherapy were similar to those reported in patients receiving  
346 ZOFTRAN Tablets and concurrent chemotherapy. The most frequently reported adverse events  
347 were headache, constipation, and diarrhea.

348 **Postoperative Nausea and Vomiting:** The adverse events in Table 7 have been reported in  
349  $\geq 5\%$  of patients receiving ZOFTRAN Tablets at a dosage of 16 mg orally in clinical trials. With the  
350 exception of headache, rates of these events were not significantly different in the ondansetron and  
351 placebo groups. These patients were receiving multiple concomitant perioperative and  
352 postoperative medications.

353

354 **Table 7. Frequency of Adverse Events From Controlled Studies With ZOFTRAN Tablets**  
355 **(Postoperative Nausea and Vomiting)**

Adverse Event	Ondansetron 16 mg (n = 550)	Placebo (n = 531)
Wound problem	152 (28%)	162 (31%)
Drowsiness/sedation	112 (20%)	122 (23%)
Headache	49 (9%)	27 (5%)
Hypoxia	49 (9%)	35 (7%)
Pyrexia	45 (8%)	34 (6%)
Dizziness	36 (7%)	34 (6%)
Gynecological disorder	36 (7%)	33 (6%)
Anxiety/agitation	33 (6%)	29 (5%)
Bradycardia	32 (6%)	30 (6%)
Shiver(s)	28 (5%)	30 (6%)
Urinary retention	28 (5%)	18 (3%)
Hypotension	27 (5%)	32 (6%)
Pruritus	27 (5%)	20 (4%)

356

357 Preliminary observations in a small number of subjects suggest a higher incidence of  
358 headache when ZOFTRAN ODT Orally Disintegrating Tablets are taken with water, when  
359 compared to without water.

360 **Observed During Clinical Practice:** In addition to adverse events reported from clinical  
361 trials, the following events have been identified during post-approval use of oral formulations of  
362 ZOFTRAN. Because they are reported voluntarily from a population of unknown size, estimates of  
363 frequency cannot be made. The events have been chosen for inclusion due to a combination of  
364 their seriousness, frequency of reporting, or potential causal connection to ZOFTRAN.

365 **General:** Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g.,  
366 anaphylaxis/anaphylactoid reactions, angioedema, bronchospasm, shortness of breath,  
367 hypotension, laryngeal edema, stridor) have also been reported. Laryngospasm, shock, and  
368 cardiopulmonary arrest have occurred during allergic reactions in patients receiving injectable  
369 ondansetron.

370 **Hepatobiliary:** Liver enzyme abnormalities

371 **Lower Respiratory:** Hiccups

372 **Neurology:** Oculogyric crisis, appearing alone, as well as with other dystonic reactions

373 **Skin:** Urticaria

## 374 **DRUG ABUSE AND DEPENDENCE**

375 Animal studies have shown that ondansetron is not discriminated as a benzodiazepine nor does  
376 it substitute for benzodiazepines in direct addiction studies.

## 377 **OVERDOSAGE**

378 There is no specific antidote for ondansetron overdose. Patients should be managed with  
379 appropriate supportive therapy. Individual intravenous doses as large as 150 mg and total daily  
380 intravenous doses as large as 252 mg have been inadvertently administered without significant  
381 adverse events. These doses are more than 10 times the recommended daily dose.

382 In addition to the adverse events listed above, the following events have been described in the  
383 setting of ondansetron overdose: “Sudden blindness” (amaurosis) of 2 to 3 minutes’ duration plus  
384 severe constipation occurred in 1 patient that was administered 72 mg of ondansetron  
385 intravenously as a single dose. Hypotension (and faintness) occurred in a patient that took 48 mg  
386 of ZOFTRAN Tablets. Following infusion of 32 mg over only a 4-minute period, a vasovagal  
387 episode with transient second-degree heart block was observed. In all instances, the events  
388 resolved completely.

## 389 **DOSAGE AND ADMINISTRATION**

390 **Instructions for Use/Handling ZOFTRAN ODT Orally Disintegrating Tablets:** Do not  
391 attempt to push ZOFTRAN ODT Tablets through the foil backing. With dry hands, PEEL BACK  
392 the foil backing of 1 blister and GENTLY remove the tablet. IMMEDIATELY place the  
393 ZOFTRAN ODT Tablet on top of the tongue where it will dissolve in seconds, then swallow with  
394 saliva. Administration with liquid is not necessary.

395 **Prevention of Nausea and Vomiting Associated With Highly Emetogenic Cancer**  
396 **Chemotherapy:** The recommended adult oral dosage of ZOFTRAN is a single 24-mg tablet  
397 administered 30 minutes before the start of single-day highly emetogenic chemotherapy, including  
398 cisplatin  $\geq 50$  mg/m<sup>2</sup>. Multiday, single-dose administration of ZOFTRAN 24-mg Tablets has not  
399 been studied.

400 **Pediatric Use:** There is no experience with the use of 24-mg ZOFTRAN Tablets in pediatric  
401 patients.

402 **Geriatric Use:** The dosage recommendation is the same as for the general population.

403 **Prevention of Nausea and Vomiting Associated With Moderately Emetogenic**  
404 **Cancer Chemotherapy:** The recommended adult oral dosage is one 8-mg ZOFTRAN Tablet or  
405 one 8-mg ZOFTRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of  
406 ZOFTRAN Oral Solution given twice a day. The first dose should be administered 30 minutes  
407 before the start of emetogenic chemotherapy, with a subsequent dose 8 hours after the first dose.  
408 One 8-mg ZOFTRAN Tablet or one 8-mg ZOFTRAN ODT Tablet or 10 mL (2 teaspoonfuls  
409 equivalent to 8 mg of ondansetron) of ZOFTRAN Oral Solution should be administered twice a day  
410 (every 12 hours) for 1 to 2 days after completion of chemotherapy.

411 **Pediatric Use:** For pediatric patients 12 years of age and older, the dosage is the same as for  
412 adults. For pediatric patients 4 through 11 years of age, the dosage is one 4-mg ZOFTRAN Tablet  
413 or one 4-mg ZOFTRAN ODT Tablet or 5 mL (1 teaspoonful equivalent to 4 mg of ondansetron) of  
414 ZOFTRAN Oral Solution given 3 times a day. The first dose should be administered 30 minutes  
415 before the start of emetogenic chemotherapy, with subsequent doses 4 and 8 hours after the first  
416 dose. One 4-mg ZOFTRAN Tablet or one 4-mg ZOFTRAN ODT Tablet or 5 mL (1 teaspoonful  
417 equivalent to 4 mg of ondansetron) of ZOFTRAN Oral Solution should be administered 3 times a  
418 day (every 8 hours) for 1 to 2 days after completion of chemotherapy.

419 **Geriatric Use:** The dosage is the same as for the general population.

420 **Prevention of Nausea and Vomiting Associated With Radiotherapy, Either Total**  
421 **Body Irradiation, or Single High-Dose Fraction or Daily Fractions to the Abdomen:**

422 The recommended oral dosage is one 8-mg ZOFTRAN Tablet or one 8-mg ZOFTRAN ODT  
423 Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFTRAN Oral Solution  
424 given 3 times a day.

425 *For total body irradiation,* one 8-mg ZOFTRAN Tablet or one 8-mg ZOFTRAN ODT Tablet or  
426 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFTRAN Oral Solution should be  
427 administered 1 to 2 hours before each fraction of radiotherapy administered each day.

428 *For single high-dose fraction radiotherapy to the abdomen,* one 8-mg ZOFTRAN Tablet or one  
429 8-mg ZOFTRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of  
430 ZOFTRAN Oral Solution should be administered 1 to 2 hours before radiotherapy, with subsequent  
431 doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy.

432 *For daily fractionated radiotherapy to the abdomen,* one 8-mg ZOFTRAN Tablet or one 8-mg  
433 ZOFTRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFTRAN

434 Oral Solution should be administered 1 to 2 hours before radiotherapy, with subsequent doses  
435 every 8 hours after the first dose for each day radiotherapy is given.

436 **Pediatric Use:** There is no experience with the use of ZOFRAN Tablets, ZOFRAN ODT  
437 Tablets, or ZOFRAN Oral Solution in the prevention of radiation-induced nausea and vomiting  
438 in pediatric patients.

439 **Geriatric Use:** The dosage recommendation is the same as for the general population.

440 **Postoperative Nausea and Vomiting:** The recommended dosage is 16 mg given as two 8-mg  
441 ZOFRAN Tablets or two 8-mg ZOFRAN ODT Tablets or 20 mL (4 teaspoonfuls equivalent to  
442 16 mg of ondansetron) of ZOFRAN Oral Solution 1 hour before induction of anesthesia.

443 **Pediatric Use:** There is no experience with the use of ZOFRAN Tablets, ZOFRAN ODT  
444 Tablets, or ZOFRAN Oral Solution in the prevention of postoperative nausea and vomiting in  
445 pediatric patients.

446 **Geriatric Use:** The dosage is the same as for the general population.

447 **Dosage Adjustment for Patients With Impaired Renal Function:** The dosage  
448 recommendation is the same as for the general population. There is no experience beyond first-day  
449 administration of ondansetron.

450 **Dosage Adjustment for Patients With Impaired Hepatic Function:** In patients with  
451 severe hepatic impairment (Child-Pugh<sup>2</sup> score of 10 or greater), clearance is reduced and apparent  
452 volume of distribution is increased with a resultant increase in plasma half-life. In such patients, a  
453 total daily dose of 8 mg should not be exceeded.

## 454 HOW SUPPLIED

455 ZOFRAN Tablets, 4 mg (ondansetron HCl dihydrate equivalent to 4 mg of ondansetron), are  
456 white, oval, film-coated tablets engraved with "Zofran" on one side and "4" on the other in daily  
457 unit dose packs of 3 tablets (NDC 0173-0446-04), bottles of 30 tablets (NDC 0173-0446-00), and  
458 unit dose packs of 100 tablets (NDC 0173-0446-02).

459 ZOFRAN Tablets, 8 mg (ondansetron HCl dihydrate equivalent to 8 mg of ondansetron), are  
460 yellow, oval, film-coated tablets engraved with "Zofran" on one side and "8" on the other in daily  
461 unit dose packs of 3 tablets (NDC 0173-0447-04), bottles of 30 tablets (NDC 0173-0447-00), and  
462 unit dose packs of 100 tablets (NDC 0173-0447-02).

463 **Bottles: Store between 2° and 30°C (36° and 86°F). Protect from light. Dispense in tight,  
464 light-resistant container as defined in the USP.**

465 **Unit Dose Packs: Store between 2° and 30°C (36° and 86°F). Protect from light. Store  
466 blisters in cartons.**

467 ZOFRAN Tablets, 24 mg (ondansetron HCl dihydrate equivalent to 24 mg of ondansetron), are  
468 pink, oval, film-coated tablets engraved with "GX CF7" on one side and "24" on the other in daily  
469 unit dose packs of 1 tablet (NDC 0173-0680-00)

470 **Store between 2° and 30°C (36° and 86°F).**

471 ZOFTRAN ODT Orally Disintegrating Tablets, 4 mg (as 4 mg ondansetron base) are white,  
472 round and plano-convex tablets debossed with a “Z4” on one side in unit dose packs of 30 tablets  
473 (NDC 0173-0569-00).

474 ZOFTRAN ODT Orally Disintegrating Tablets, 8 mg (as 8 mg ondansetron base) are white,  
475 round and plano-convex tablets debossed with a “Z8” on one side in unit dose packs of 10 tablets  
476 (NDC 0173-0570-04) and 30 tablets (NDC 0173-0570-00).

477 **Store between 2° and 30°C (36° and 86°F).**

478 ZOFTRAN Oral Solution, a clear, colorless to light yellow liquid with a characteristic  
479 strawberry odor, contains 5 mg of ondansetron HCl dihydrate equivalent to 4 mg of ondansetron  
480 per 5 mL in amber glass bottles of 50 mL with child-resistant closures (NDC 0173-0489-00).

481 **Store upright between 15° and 30°C (59° and 86°F). Protect from light. Store bottles**  
482 **upright in cartons.**

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496

497 ZOFTRAN Tablets and Oral Solution:

498 GlaxoSmithKline

499 Research Triangle Park, NC 27709

500

501 ZOFTRAN ODT Orally Disintegrating Tablets:

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