

PRESCRIBING INFORMATION

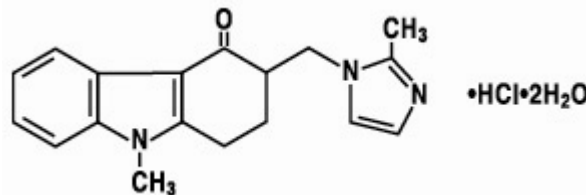
ZOFRAN[®]
(ondansetron hydrochloride)
Tablets

ZOFRAN ODT[®]
(ondansetron)
Orally Disintegrating Tablets

ZOFRAN[®]
(ondansetron hydrochloride)
Oral Solution

DESCRIPTION

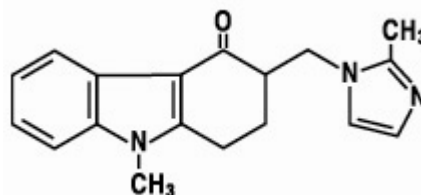
The active ingredient in ZOFRAN[®] Tablets and ZOFRAN[®] Oral Solution is ondansetron hydrochloride (HCl) as the dihydrate, the racemic form of ondansetron and a selective blocking agent of the serotonin 5-HT₃ receptor type. Chemically it is (±) 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, monohydrochloride, dihydrate. It has the following structural formula:



The empirical formula is C₁₈H₁₉N₃O·HCl·2H₂O, 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-HT₃ 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

32 The empirical formula is C₁₈H₁₉N₃O representing a molecular weight of 293.4.

33

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

38

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.

45

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.

48 CLINICAL PHARMACOLOGY

49

50 **Pharmacodynamics:** Ondansetron is a selective 5-HT₃ 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-HT₃ 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-HT₃ receptors and initiate the
59 vomiting reflex.

59

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-HT₃ receptor antagonist.

62

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.

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

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

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

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

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

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

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

101

102 **Table 1. Pharmacokinetics in Normal Volunteers: Single 8-mg ZOFRAN 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

103

104 **Table 2. Pharmacokinetics in Normal Volunteers: Single 24-mg ZOFRAN 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

105

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

111 In patients with mild-to-moderate hepatic impairment, clearance is reduced 2-fold and mean
112 half-life is increased to 11.6 hours compared to 5.7 hours in normals. In patients with severe
113 hepatic impairment (Child-Pugh² score of 10 or greater), clearance is reduced 2-fold to 3-fold and
114 apparent volume of distribution is increased with a resultant increase in half-life to 20 hours. In
115 patients with severe hepatic impairment, a total daily dose of 8 mg should not be exceeded.

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

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

124 Four- and 8-mg doses of either ZOFRAN Oral Solution or ZOFRAN ODT Orally
125 Disintegrating Tablets are bioequivalent to corresponding doses of ZOFRAN Tablets and may be

126 used interchangeably. One 24-mg ZOFTRAN Tablet is bioequivalent to and interchangeable with
127 three 8-mg ZOFTRAN Tablets.

128 **CLINICAL TRIALS**

129 **Chemotherapy-Induced Nausea and Vomiting: *Highly Emetogenic Chemotherapy:***

130 In 2 randomized, double-blind, monotherapy trials, a single 24-mg ZOFTRAN Tablet was superior
131 to a relevant historical placebo control in the prevention of nausea and vomiting associated with
132 highly emetogenic cancer chemotherapy, including cisplatin ≥ 50 mg/m². Steroid administration
133 was excluded from these clinical trials. More than 90% of patients receiving a cisplatin dose \geq
134 50 mg/m² in the historical placebo comparator experienced vomiting in the absence of antiemetic
135 therapy.

136 The first trial compared oral doses of ondansetron 24 mg once a day, 8 mg twice a day, and
137 32 mg once a day in 357 adult cancer patients receiving chemotherapy regimens containing
138 cisplatin ≥ 50 mg/m². A total of 66% of patients in the ondansetron 24-mg once-a-day group, 55%
139 in the ondansetron 8-mg twice-a-day group, and 55% in the ondansetron 32-mg once-a-day group
140 completed the 24-hour study period with 0 emetic episodes and no rescue antiemetic medications,
141 the primary endpoint of efficacy. Each of the 3 treatment groups was shown to be statistically
142 significantly superior to a historical placebo control.

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

146 In a second trial, efficacy of the oral ondansetron 24-mg once-a-day regimen in the prevention
147 of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including
148 cisplatin ≥ 50 mg/m², was confirmed.

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

154

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

	Ondansetron 8-mg b.i.d. ZOFTRAN Tablets ^a	Placebo	<i>P</i> 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%)	
Median number of emetic episodes	0.0	Undefined ^b	
Median time to first emetic episode (h)	Undefined ^c	6.5	

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

159 ^b Median undefined since at least 50% of the patients were withdrawn or had more than 2 emetic
160 episodes.

161 ^c Median undefined since at least 50% of patients did not have any emetic episodes.

162

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

168

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

	Ondansetron	
	8-mg b.i.d. ZOFTRAN Tablets ^a	8-mg t.i.d. ZOFTRAN Tablets ^b
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 ^c	Undefined ^c
Median nausea scores (0-100) ^d	6	6

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

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

176 ^c Median undefined since at least 50% of patients did not have any emetic episodes.

177 ^d Visual analog scale assessment: 0 = no nausea, 100 = nausea as bad as it can be.

178

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

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

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

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

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

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

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

227 **INDICATIONS AND USAGE**

- 228 1. Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy,
229 including cisplatin $\geq 50 \text{ mg/m}^2$.
- 230 2. Prevention of nausea and vomiting associated with initial and repeat courses of moderately
231 emetogenic cancer chemotherapy.

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

241 **CONTRAINDICATIONS**

242 The concomitant use of apomorphine with ondansetron is contraindicated based on reports of
243 profound hypotension and loss of consciousness when apomorphine was administered with
244 ondansetron.

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

247 **WARNINGS**

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

250 ECG changes including QT interval prolongation has been seen in patients receiving
251 ondansetron. In addition, post-marketing cases of Torsade de Pointes have been reported in
252 patients using ondansetron. Avoid ZOFTRAN in patients with congenital long QT syndrome. ECG
253 monitoring is recommended in patients with electrolyte abnormalities (e.g., hypokalemia or
254 hypomagnesemia), congestive heart failure, bradyarrhythmias or patients taking other medicinal
255 products that lead to QT prolongation.

256 The development of serotonin syndrome has been reported with 5-HT₃ receptor antagonists
257 alone. Most reports have been associated with concomitant use of serotonergic drugs (e.g.,
258 selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors
259 (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and
260 intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome
261 occurring with overdose of ZOFTRAN alone has also been reported. The majority of reports of
262 serotonin syndrome related to 5-HT₃ receptor antagonist use occurred in a post-anesthesia care
263 unit or an infusion center.

264 Symptoms associated with serotonin syndrome may include the following combination of
265 signs and symptoms: mental status changes (e.g., agitation, hallucinations, delirium, and coma),
266 autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing,
267 hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia,
268 incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting,
269 diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with
270 concomitant use of ZOFTRAN and other serotonergic drugs. If symptoms of serotonin syndrome

271 occur, discontinue ZOFTRAN and initiate supportive treatment. Patients should be informed of
272 the increased risk of serotonin syndrome, especially if ZOFTRAN is used concomitantly with
273 other serotonergic drugs (see PRECAUTIONS and OVERDOSAGE).

274 **PRECAUTIONS**

275 **General:** Ondansetron is not a drug that stimulates gastric or intestinal peristalsis. It should not
276 be used instead of nasogastric suction. The use of ondansetron in patients following abdominal
277 surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive
278 ileus and/or gastric distension.

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

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

288 ***Serotonin Syndrome:*** Advise patients of the possibility of serotonin syndrome with
289 concomitant use of ZOFTRAN and another serotonergic agent such as medications to treat
290 depression and migraines. Advise patients to seek immediate medical attention if the following
291 symptoms occur: changes in mental status, autonomic instability, neuromuscular symptoms with
292 or without gastrointestinal symptoms.

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

299 ***Apomorphine:*** Based on reports of profound hypotension and loss of consciousness when
300 apomorphine was administered with ondansetron, concomitant use of apomorphine with
301 ondansetron is contraindicated (see CONTRAINDICATIONS).

302 ***Phenytoin, Carbamazepine, and Rifampicin:*** In patients treated with potent inducers of
303 CYP3A4 (i.e., phenytoin, carbamazepine, and rifampicin), the clearance of ondansetron was
304 significantly increased and ondansetron blood concentrations were decreased. However, on the
305 basis of available data, no dosage adjustment for ondansetron is recommended for patients on
306 these drugs.^{1,3}

307 ***Serotonergic Drugs:*** Serotonin syndrome (including altered mental status, autonomic
308 instability, and neuromuscular symptoms) has been described following the concomitant use of
309 5-HT₃ receptor antagonists and other serotonergic drugs, including selective serotonin reuptake

310 inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) (see
311 WARNINGS).

312 **Tramadol:** Although no pharmacokinetic drug interaction between ondansetron and tramadol
313 has been observed, data from 2 small studies indicate that ondansetron may be associated with an
314 increase in patient controlled administration of tramadol.^{4,5}

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

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

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

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

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

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

336 **Pediatric Use:** Little information is available about dosage in pediatric patients 4 years of age or
337 younger (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION
338 sections for use in pediatric patients 4 to 18 years of age).

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

346 **ADVERSE REACTIONS**

347 The following have been reported as adverse events in clinical trials of patients treated with
348 ondansetron, the active ingredient of ZOFTRAN. A causal relationship to therapy with ZOFTRAN
349 has been unclear in many cases.

350 **Chemotherapy-Induced Nausea and Vomiting:** The adverse events in Table 5 have been
351 reported in $\geq 5\%$ of adult patients receiving a single 24-mg ZOFTRAN Tablet in 2 trials. These
352 patients were receiving concurrent highly emetogenic cisplatin-based chemotherapy regimens
353 (cisplatin dose $\geq 50 \text{ mg/m}^2$).

354
355 **Table 5. Principal Adverse Events in US Trials: Single Day Therapy With 24-mg ZOFTRAN**
356 **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%)

357
358 The adverse events in Table 6 have been reported in $\geq 5\%$ of adults receiving either 8 mg of
359 ZOFTRAN Tablets 2 or 3 times a day for 3 days or placebo in 4 trials. These patients were
360 receiving concurrent moderately emetogenic chemotherapy, primarily cyclophosphamide-based
361 regimens.

362
363 **Table 6. Principal Adverse Events in US Trials: 3 Days of Therapy With 8-mg ZOFTRAN**
364 **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%)

365
366 **Central Nervous System:** There have been rare reports consistent with, but not diagnostic
367 of, extrapyramidal reactions in patients receiving ondansetron.

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

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

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

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

379 **Other:** Rare cases of anaphylaxis, bronchospasm, tachycardia, angina (chest pain),
380 hypokalemia, electrocardiographic alterations, vascular occlusive events, and grand mal seizures
381 have been reported. Except for bronchospasm and anaphylaxis, the relationship to ZOFRAN was
382 unclear.

383 **Radiation-Induced Nausea and Vomiting:** The adverse events reported in patients receiving
384 ZOFRAN Tablets and concurrent radiotherapy were similar to those reported in patients receiving
385 ZOFRAN Tablets and concurrent chemotherapy. The most frequently reported adverse events
386 were headache, constipation, and diarrhea.

387 **Postoperative Nausea and Vomiting:** The adverse events in Table 7 have been reported in \geq
388 5% of patients receiving ZOFRAN Tablets at a dosage of 16 mg orally in clinical trials. With the
389 exception of headache, rates of these events were not significantly different in the ondansetron and
390 placebo groups. These patients were receiving multiple concomitant perioperative and
391 postoperative medications.

392

393 **Table 7. Frequency of Adverse Events From Controlled Studies With ZOFRAN Tablets**
394 **(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%)

395

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

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

404 **Cardiovascular:** Rarely and predominantly with intravenous ondansetron, transient ECG
405 changes including QT interval prolongation have been reported.

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

411 **Hepatobiliary:** Liver enzyme abnormalities

412 **Lower Respiratory:** Hiccups

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

414 **Skin:** Urticaria, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

415 **Special Senses: Eye Disorders:** Cases of transient blindness, predominantly during
416 intravenous administration, have been reported. These cases of transient blindness were reported
417 to resolve within a few minutes up to 48 hours.

418 **DRUG ABUSE AND DEPENDENCE**

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

421 **OVERDOSAGE**

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

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

433 Pediatric cases consistent with serotonin syndrome have been reported after inadvertent oral
434 overdoses of ondansetron (exceeding estimated ingestion of 5 mg/kg) in young children. Reported

435 symptoms included somnolence, agitation, tachycardia, tachypnea, hypertension, flushing,
436 mydriasis, diaphoresis, myoclonic movements, horizontal nystagmus, hyperreflexia, and seizure.
437 Patients required supportive care, including intubation in some cases, with complete recovery
438 without sequelae within 1 to 2 days.

439 **DOSAGE AND ADMINISTRATION**

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

445 **Prevention of Nausea and Vomiting Associated With Highly Emetogenic Cancer**
446 **Chemotherapy:** The recommended adult oral dosage of ZOFTRAN is 24 mg given as three 8-mg
447 tablets administered 30 minutes before the start of single-day highly emetogenic chemotherapy,
448 including cisplatin ≥ 50 mg/m². Multiday, single-dose administration of a 24 mg dosage has not
449 been studied.

450 **Pediatric Use:** There is no experience with the use of a 24 mg dosage in pediatric patients.

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

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

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

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

469 **Prevention of Nausea and Vomiting Associated With Radiotherapy, Either Total**
470 **Body Irradiation, or Single High-Dose Fraction or Daily Fractions to the Abdomen:**
471 The recommended oral dosage is one 8-mg ZOFTRAN Tablet or one 8-mg ZOFTRAN ODT Tablet
472 or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFTRAN Oral Solution given
473 3 times a day.

474 *For total body irradiation, one 8-mg ZOFTRAN Tablet or one 8-mg ZOFTRAN ODT Tablet or*
475 *10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFTRAN Oral Solution should be*
476 *administered 1 to 2 hours before each fraction of radiotherapy administered each day.*

477 *For single high-dose fraction radiotherapy to the abdomen, one 8-mg ZOFTRAN Tablet or one*
478 *8-mg ZOFTRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of*
479 *ZOFTRAN Oral Solution should be administered 1 to 2 hours before radiotherapy, with subsequent*
480 *doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy.*

481 *For daily fractionated radiotherapy to the abdomen, one 8-mg ZOFTRAN Tablet or one 8-mg*
482 *ZOFTRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFTRAN*
483 *Oral Solution should be administered 1 to 2 hours before radiotherapy, with subsequent doses*
484 *every 8 hours after the first dose for each day radiotherapy is given.*

485 **Pediatric Use:** There is no experience with the use of ZOFTRAN Tablets, ZOFTRAN ODT
486 Tablets, or ZOFTRAN Oral Solution in the prevention of radiation-induced nausea and vomiting
487 in pediatric patients.

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

489 **Postoperative Nausea and Vomiting:** The recommended dosage is 16 mg given as two 8-mg
490 ZOFTRAN Tablets or two 8-mg ZOFTRAN ODT Tablets or 20 mL (4 teaspoonfuls equivalent to
491 16 mg of ondansetron) of ZOFTRAN Oral Solution 1 hour before induction of anesthesia.

492 **Pediatric Use:** There is no experience with the use of ZOFTRAN Tablets, ZOFTRAN ODT
493 Tablets, or ZOFTRAN Oral Solution in the prevention of postoperative nausea and vomiting in
494 pediatric patients.

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

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

499 **Dosage Adjustment for Patients With Impaired Hepatic Function:** In patients with
500 severe hepatic impairment (Child-Pugh² score of 10 or greater), clearance is reduced and apparent
501 volume of distribution is increased with a resultant increase in plasma half-life. In such patients, a
502 total daily dose of 8 mg should not be exceeded.

503 HOW SUPPLIED

504 ZOFTRAN Tablets, 4 mg (ondansetron HCl dihydrate equivalent to 4 mg of ondansetron), are
505 white, oval, film-coated tablets engraved with “Zofran” on one side and “4” on the other in bottles
506 of 30 tablets (NDC 0173-0446-00).

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

509 ZOFTRAN Tablets, 8 mg (ondansetron HCl dihydrate equivalent to 8 mg of ondansetron), are
510 yellow, oval, film-coated tablets engraved with “Zofran” on one side and “8” on the other in daily
511 unit dose packs of 3 tablets (NDC 0173-0447-04), and bottles of 30 tablets (NDC 0173-0447-00).

512 **Bottles: Store between 2° and 30°C (36° and 86°F). Dispense in tight container as defined**
513 **in the USP.**

514 **Unit Dose Packs: Store between 2° and 30°C (36° and 86°F).**

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

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

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

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

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

527 REFERENCES

- 528 1. Britto MR, Hussey EK, Mydlow P, et al. Effect of enzyme inducers on ondansetron (OND)
529 metabolism in humans. *Clin Pharmacol Ther.* 1997;61:228.
- 530 2. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the
531 oesophagus for bleeding oesophageal varices. *Brit J Surg.* 1973;60:646-649.
- 532 3. Villikka K, Kivisto KT, Neuvonen PJ. The effect of rifampin on the pharmacokinetics of oral
533 and intravenous ondansetron. *Clin Pharmacol Ther.* 1999;65:377-381.
- 534 4. De Witte JL, Schoenmaekers B, Sessler DI, et al. *Anesth Analg.* 2001;92:1319-1321.
- 535 5. Arcioni R, della Rocca M, Romanò R, et al. *Anesth Analg.* 2002;94:1553-1557.

536
537



538

539 GlaxoSmithKline

540 Research Triangle Park, NC 27709

541

542 ZOFTRAN Tablets and Oral Solution:

543 GlaxoSmithKline

544 Research Triangle Park, NC 27709

545

546 ZOFTRAN ODT Orally Disintegrating Tablets:

547 Manufactured for GlaxoSmithKline

548 Research Triangle Park, NC 27709

549 by Catalent UK Swindon Zydis Ltd.

550 Blagrove, Swindon, Wiltshire, UK SN5 8RU

551
552 ©Year, the GSK group of companies. All rights reserved.
553
554 September 2014
555 ZFT:xPI