

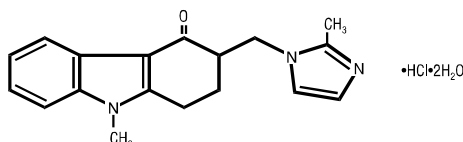
1 PRESCRIBING INFORMATION

2 **ZOFRAN[®]**
3 **(ondansetron hydrochloride)**
4 **Injection**

5
6 **ZOFRAN[®]**
7 **(ondansetron hydrochloride)**
8 **Injection Premixed**

9 **DESCRIPTION**

10 The active ingredient in ZOFRAN Injection and ZOFRAN Injection Premixed is ondansetron
11 hydrochloride (HCl), the racemic form of ondansetron and a selective blocking agent of the
12 serotonin 5-HT₃ receptor type. Chemically it is (±) 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-
13 1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, monohydrochloride, dihydrate. It has the
14 following structural formula:
15



18 The empirical formula is C₁₈H₁₉N₃O•HCl•2H₂O, representing a molecular weight of 365.9.

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

20 **Sterile Injection for Intravenous (I.V.) or Intramuscular (I.M.) Administration:** Each
21 1 mL of aqueous solution in the 2-mL single-dose vial contains 2 mg of ondansetron as the
22 hydrochloride dihydrate; 9.0 mg of sodium chloride, USP; and 0.5 mg of citric acid
23 monohydrate, USP and 0.25 mg of sodium citrate dihydrate, USP as buffers in Water for
24 Injection, USP.

25 Each 1 mL of aqueous solution in the 20-mL multidose vial contains 2 mg of ondansetron as
26 the hydrochloride dihydrate; 8.3 mg of sodium chloride, USP; 0.5 mg of citric acid monohydrate,
27 USP and 0.25 mg of sodium citrate dihydrate, USP as buffers; and 1.2 mg of methylparaben, NF
28 and 0.15 mg of propylparaben, NF as preservatives in Water for Injection, USP.

29 ZOFRAN Injection is a clear, colorless, nonpyrogenic, sterile solution. The pH of the injection
30 solution is 3.3 to 4.0.

31 **Sterile, Premixed Solution for Intravenous Administration in Single-Dose, Flexible**
32 **Plastic Containers:** Each 50 mL contains ondansetron 32 mg (as the hydrochloride dihydrate);
33 dextrose 2,500 mg; and citric acid 26 mg and sodium citrate 11.5 mg as buffers in Water for
34 Injection, USP. It contains no preservatives. The osmolarity of this solution is 270 mOsm/L
35 (approx.), and the pH is 3.0 to 4.0.

36 The flexible plastic container is fabricated from a specially formulated, nonplasticized,
37 thermoplastic co-polyester (CR3). Water can permeate from inside the container into the
38 overwrap but not in amounts sufficient to affect the solution significantly. Solutions inside the
39 plastic container also can leach out certain of the chemical components in very small amounts
40 before the expiration period is attained. However, the safety of the plastic has been confirmed by
41 tests in animals according to USP biological standards for plastic containers.

42 **CLINICAL PHARMACOLOGY**

43 **Pharmacodynamics:** Ondansetron is a selective 5-HT₃ receptor antagonist. While
44 ondansetron's mechanism of action has not been fully characterized, it is not a dopamine-receptor
45 antagonist. Serotonin receptors of the 5-HT₃ type are present both peripherally on vagal nerve
46 terminals and centrally in the chemoreceptor trigger zone of the area postrema. It is not certain
47 whether ondansetron's antiemetic action in chemotherapy-induced emesis is mediated centrally,
48 peripherally, or in both sites. However, cytotoxic chemotherapy appears to be associated with
49 release of serotonin from the enterochromaffin cells of the small intestine. In humans, urinary
50 5-HIAA (5-hydroxyindoleacetic acid) excretion increases after cisplatin administration in parallel
51 with the onset of emesis. The released serotonin may stimulate the vagal afferents through the
52 5-HT₃ receptors and initiate the vomiting reflex.

53 In animals, the emetic response to cisplatin can be prevented by pretreatment with an inhibitor
54 of serotonin synthesis, bilateral abdominal vagotomy and greater splanchnic nerve section, or
55 pretreatment with a serotonin 5-HT₃ receptor antagonist.

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

63 In a gender-balanced pharmacodynamic study (n = 56), ondansetron 4 mg administered
64 intravenously or intramuscularly was dynamically similar in the prevention of emesis and nausea
65 using the ipecacuanha model of emesis. Both treatments were well tolerated.

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 extensively metabolized in humans, with approximately
70 5% of a radiolabeled dose recovered as the parent compound from the urine. The primary
71 metabolic pathway is hydroxylation on the indole ring followed by glucuronide or sulfate
72 conjugation.

73 Although some nonconjugated metabolites have pharmacologic activity, these are not found
74 in plasma at concentrations likely to significantly contribute to the biological activity of
75 ondansetron.

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

86 In normal volunteers, the following mean pharmacokinetic data have been determined
87 following a single 0.15-mg/kg I.V. dose.

88

89 **Table 1. Pharmacokinetics in Normal Volunteers**

Age-group	n	Peak Plasma Concentration (ng/mL)	Mean Elimination Half-life (h)	Plasma Clearance (L/h/kg)
19-40	11	102	3.5	0.381
61-74	12	106	4.7	0.319
≥75	11	170	5.5	0.262

90

91 A reduction in clearance and increase in elimination half-life are seen in patients over 75 years
92 of age. In clinical trials with cancer patients, safety and efficacy were similar in patients over 65
93 years of age and those under 65 years of age; there was an insufficient number of patients over
94 75 years of age to permit conclusions in that age-group. No dosage adjustment is recommended
95 in the elderly.

96 In patients with mild-to-moderate hepatic impairment, clearance is reduced twofold and mean
97 half-life is increased to 11.6 hours compared to 5.7 hours in normals. In patients with severe
98 hepatic impairment (Child-Pugh score¹ of 10 or greater), clearance is reduced twofold to threefold
99 and apparent volume of distribution is increased with a resultant increase in half-life to 20 hours.
100 In patients with severe hepatic impairment, a total daily dose of 8 mg should not be exceeded.

101 Due to the very small contribution (5%) of renal clearance to the overall clearance, renal
102 impairment was not expected to significantly influence the total clearance of ondansetron.
103 However, ondansetron mean plasma clearance was reduced by about 41% in patients with severe
104 renal impairment (creatinine clearance <30 mL/min). This reduction in clearance is variable and

105 was not consistent with an increase in half-life. No reduction in dose or dosing frequency in
106 these patients is warranted.

107 In adult cancer patients, the mean elimination half-life was 4.0 hours, and there was no
108 difference in the multidose pharmacokinetics over a 4-day period. In a study of 21 pediatric
109 cancer patients (aged 4 to 18 years) who received three I.V. doses of 0.15 mg/kg of ondansetron
110 at 4-hour intervals, patients older than 15 years of age exhibited ondansetron pharmacokinetic
111 parameters similar to those of adults. Patients aged 4 to 12 years generally showed higher
112 clearance and somewhat larger volume of distribution than adults. Most pediatric patients
113 younger than 15 years of age with cancer had a shorter (2.4 hours) ondansetron plasma half-life
114 than patients older than 15 years of age. It is not known whether these differences in ondansetron
115 plasma half-life may result in differences in efficacy between adults and some young pediatric
116 patients (see CLINICAL TRIALS: Pediatric Studies).

117 In a study of 21 pediatric patients (aged 3 to 12 years) who were undergoing surgery requiring
118 anesthesia for a duration of 45 minutes to 2 hours, a single I.V. dose of ondansetron, 2 mg (3 to
119 7 years) or 4 mg (8 to 12 years), was administered immediately prior to anesthesia induction.
120 Mean weight-normalized clearance and volume of distribution values in these pediatric surgical
121 patients were similar to those previously reported for young adults. Mean terminal half-life was
122 slightly reduced in pediatric patients (range, 2.5 to 3 hours) in comparison with adults (range, 3 to
123 3.5 hours).

124 In normal volunteers (19 to 39 years old, n = 23), the peak plasma concentration was
125 264 ng/mL following a single 32-mg dose administered as a 15-minute I.V. infusion. The mean
126 elimination half-life was 4.1 hours. Systemic exposure to 32 mg of ondansetron was not
127 proportional to dose as measured by comparing dose-normalized AUC values to an 8-mg dose.
128 This is consistent with a small decrease in systemic clearance with increasing plasma
129 concentrations.

130 A study was performed in normal volunteers (n = 56) to evaluate the pharmacokinetics of a
131 single 4-mg dose administered as a 5-minute infusion compared to a single intramuscular
132 injection. Systemic exposure as measured by mean AUC was equivalent, with values of 156
133 [95% CI 136, 180] and 161 [95% CI 137, 190] ng•h/mL for I.V. and I.M. groups, respectively.
134 Mean peak plasma concentrations were 42.9 [95% CI 33.8, 54.4] ng/mL at 10 minutes after I.V.
135 infusion and 31.9 [95% CI 26.3, 38.6] ng/mL at 41 minutes after I.M. injection. The mean
136 elimination half-life was not affected by route of administration.

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

140 A positive lymphoblast transformation test to ondansetron has been reported, which suggests
141 immunologic sensitivity to ondansetron.

142 **CLINICAL TRIALS**

143 **Chemotherapy-Induced Nausea and Vomiting:** In a double-blind study of three different
 144 dosing regimens of ZOFTRAN Injection, 0.015 mg/kg, 0.15 mg/kg, and 0.30 mg/kg, each given
 145 three times during the course of cancer chemotherapy, the 0.15-mg/kg dosing regimen was more
 146 effective than the 0.015-mg/kg dosing regimen. The 0.30-mg/kg dosing regimen was not shown
 147 to be more effective than the 0.15-mg/kg dosing regimen.

148 **Cisplatin-Based Chemotherapy:** In a double-blind study in 28 patients, ZOFTRAN
 149 Injection (three 0.15-mg/kg doses) was significantly more effective than placebo in preventing
 150 nausea and vomiting induced by cisplatin-based chemotherapy. Treatment response was as
 151 shown in Table 2.

152
 153 **Table 2. Prevention of Chemotherapy-Induced Nausea and Emesis in Single-Day Cisplatin**
 154 **Therapy***

	ZOFTRAN Injection	Placebo	P Value [†]
Number of patients	14	14	
Treatment response			
0 Emetic episodes	2 (14%)	0 (0%)	
1-2 Emetic episodes	8 (57%)	0 (0%)	
3-5 Emetic episodes	2 (14%)	1 (7%)	
More than 5 emetic episodes/rescued	2 (14%)	13 (93%)	0.001
Median number of emetic episodes	1.5	Undefined [‡]	
Median time to first emetic episode (h)	11.6	2.8	0.001
Median nausea scores (0-100) [§]	3	59	0.034
Global satisfaction with control of nausea and vomiting (0-100)	96	10.5	0.009

155 * Chemotherapy was high dose (100 and 120 mg/m²; ZOFTRAN Injection n = 6, placebo n = 5)
 156 or moderate dose (50 and 80 mg/m²; ZOFTRAN Injection n = 8, placebo n = 9). Other
 157 chemotherapeutic agents included fluorouracil, doxorubicin, and cyclophosphamide. There
 158 was no difference between treatments in the types of chemotherapy that would account for
 159 differences in response.

160 [†] Efficacy based on "all patients treated" analysis.

161 [‡] Median undefined since at least 50% of the patients were rescued or had more than five
 162 emetic episodes.

163 [§] Visual analog scale assessment of nausea: 0 = no nausea, 100 = nausea as bad as it can be.

164 ^{||} Visual analog scale assessment of satisfaction: 0 = not at all satisfied, 100 = totally satisfied.

165

166 Ondansetron was compared with metoclopramide in a single-blind trial in 307 patients
 167 receiving cisplatin ≥ 100 mg/m² with or without other chemotherapeutic agents. Patients received
 168 the first dose of ondansetron or metoclopramide 30 minutes before cisplatin. Two additional
 169 ondansetron doses were administered 4 and 8 hours later, or five additional metoclopramide
 170 doses were administered 2, 4, 7, 10, and 13 hours later. Cisplatin was administered over a period
 171 of 3 hours or less. Episodes of vomiting and retching were tabulated over the period of 24 hours
 172 after cisplatin. The results of this study are summarized in Table 3.

173
 174 **Table 3. Prevention of Emesis Induced by Cisplatin (≥ 100 mg/m²) Single-Day Therapy***

	ZOFRAN Injection	Metoclopramide	P Value
Dose	0.15 mg/kg x 3	2 mg/kg x 6	
Number of patients in efficacy population	136	138	
Treatment response			
0 Emetic episodes	54 (40%)	41 (30%)	
1-2 Emetic episodes	34 (25%)	30 (22%)	
3-5 Emetic episodes	19 (14%)	18 (13%)	
More than 5 emetic episodes/rescued	29 (21%)	49 (36%)	
Comparison of treatments with respect to			
0 Emetic episodes	54/136	41/138	0.083
More than 5 emetic episodes/rescued	29/136	49/138	0.009
Median number of emetic episodes	1	2	0.005
Median time to first emetic episode (h)	20.5	4.3	<0.001
Global satisfaction with control of nausea and vomiting (0-100) [†]	85	63	0.001
Acute dystonic reactions	0	8	0.005
Akathisia	0	10	0.002

175 * In addition to cisplatin, 68% of patients received other chemotherapeutic agents, including
 176 cyclophosphamide, etoposide, and fluorouracil. There was no difference between treatments
 177 in the types of chemotherapy that would account for differences in response.

178 † Visual analog scale assessment: 0 = not at all satisfied, 100 = totally satisfied.

179
 180 In a stratified, randomized, double-blind, parallel-group, multicenter study, a single 32-mg
 181 dose of ondansetron was compared with three 0.15-mg/kg doses in patients receiving cisplatin
 182 doses of either 50 to 70 mg/m² or ≥ 100 mg/m². Patients received the first ondansetron dose
 183 30 minutes before cisplatin. Two additional ondansetron doses were administered 4 and 8 hours

184 later to the group receiving three 0.15-mg/kg doses. In both strata, significantly fewer patients on
 185 the single 32-mg dose than those receiving the three-dose regimen failed.

186
 187 **Table 4. Prevention of Chemotherapy-Induced Nausea and Emesis in Single-Dose Therapy**

	0.15 mg/kg x 3	Ondansetron Dose 32 mg x 1	P Value
High-dose cisplatin (≥ 100 mg/m²)			
Number of patients	100	102	
Treatment response			
0 Emetic episodes	41 (41%)	49 (48%)	0.315
1-2 Emetic episodes	19 (19%)	25 (25%)	
3-5 Emetic episodes	4 (4%)	8 (8%)	
More than 5 emetic episodes/rescued	36 (36%)	20 (20%)	0.009
Median time to first emetic episode (h)	21.7	23	0.173
Median nausea scores (0-100)*	28	13	0.004
Medium-dose cisplatin (50-70 mg/m²)			
Number of patients	101	93	
Treatment response			
0 Emetic episodes	62 (61%)	68 (73%)	0.083
1-2 Emetic episodes	11 (11%)	14 (15%)	
3-5 Emetic episodes	6 (6%)	3 (3%)	
More than 5 emetic episodes/rescued	22 (22%)	8 (9%)	0.011
Median time to first emetic episode (h)	Undefined [†]	Undefined	
Median nausea scores (0-100)*	9	3	0.131

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

189 [†] Median undefined since at least 50% of patients did not have any emetic episodes.

190
 191 **Cyclophosphamide-Based Chemotherapy:** In a double-blind, placebo-controlled study
 192 of ZOFTRAN Injection (three 0.15-mg/kg doses) in 20 patients receiving cyclophosphamide (500
 193 to 600 mg/m²) chemotherapy, ZOFTRAN Injection was significantly more effective than placebo
 194 in preventing nausea and vomiting. The results are summarized in Table 5.

195

196 **Table 5. Prevention of Chemotherapy-Induced Nausea and Emesis in Single-Day**
 197 **Cyclophosphamide Therapy***

	ZOFRAN Injection	Placebo	<i>P</i> Value [†]
Number of patients	10	10	
Treatment response			
0 Emetic episodes	7 (70%)	0 (0%)	0.001
1-2 Emetic episodes	0 (0%)	2 (20%)	
3-5 Emetic episodes	2 (20%)	4 (40%)	
More than 5 emetic episodes/rescued	1 (10%)	4 (40%)	0.131
Median number of emetic episodes	0	4	0.008
Median time to first emetic episode (h)	Undefined [‡]	8.79	
Median nausea scores (0-100) [§]	0	60	0.001
Global satisfaction with control of nausea and vomiting (0-100)	100	52	0.008

198 * Chemotherapy consisted of cyclophosphamide in all patients, plus other agents, including
 199 fluorouracil, doxorubicin, methotrexate, and vincristine. There was no difference between
 200 treatments in the type of chemotherapy that would account for differences in response.

201 † Efficacy based on "all patients treated" analysis.

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

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

204 || Visual analog scale assessment of satisfaction: 0 = not at all satisfied, 100 = totally satisfied.

205

206 **Re-treatment:** In uncontrolled trials, 127 patients receiving cisplatin (median dose,
 207 100 mg/m²) and ondansetron who had two or fewer emetic episodes were re-treated with
 208 ondansetron and chemotherapy, mainly cisplatin, for a total of 269 re-treatment courses (median,
 209 2; range, 1 to 10). No emetic episodes occurred in 160 (59%), and two or fewer emetic episodes
 210 occurred in 217 (81%) re-treatment courses.

211 **Pediatric Studies:** Four open-label, noncomparative (one US, three foreign) trials have
 212 been performed with 209 pediatric cancer patients aged 4 to 18 years given a variety of cisplatin
 213 or noncisplatin regimens. In the three foreign trials, the initial ZOFRAN Injection dose ranged
 214 from 0.04 to 0.87 mg/kg for a total dose of 2.16 to 12 mg. This was followed by the oral
 215 administration of ondansetron ranging from 4 to 24 mg daily for 3 days. In the US trial,
 216 ZOFRAN was administered intravenously (only) in three doses of 0.15 mg/kg each for a total
 217 daily dose of 7.2 to 39 mg. In these studies, 58% of the 196 evaluable patients had a complete
 218 response (no emetic episodes) on day 1. Thus, prevention of emesis in these pediatric patients

219 was essentially the same as for patients older than 18 years of age. Overall, ZOFTRAN Injection
220 was well tolerated in these pediatric patients.

221 **Postoperative Nausea and Vomiting: *Prevention of Postoperative Nausea and***
222 ***Vomiting:*** Adult surgical patients who received ondansetron immediately before the induction
223 of general balanced anesthesia (barbiturate: thiopental, methohexital, or thiamylal; opioid:
224 alfentanil or fentanyl; nitrous oxide; neuromuscular blockade: succinylcholine/curare and/or
225 vecuronium or atracurium; and supplemental isoflurane) were evaluated in two double-blind US
226 studies involving 554 patients. ZOFTRAN Injection (4 mg) I.V. given over 2 to 5 minutes was
227 significantly more effective than placebo. The results of these studies are summarized in Table 6.
228

229 **Table 6. Prevention of Postoperative Nausea and Vomiting in Adult Patients**

	Ondansetron 4 mg I.V.	Placebo	<i>P</i> Value
Study 1			
Emetic episodes: Number of patients	136	139	
Treatment response over 24-h postoperative period			
0 Emetic episodes	103 (76%)	64 (46%)	<0.001
1 Emetic episode	13 (10%)	17 (12%)	
More than 1 emetic episode/rescued	20 (15%)	58 (42%)	
Nausea assessments: Number of patients	134	136	
No nausea over 24-h postoperative period	56 (42%)	39 (29%)	
Study 2			
Emetic episodes: Number of patients	136	143	
Treatment response over 24-h postoperative period			
0 Emetic episodes	85 (63%)	63 (44%)	0.002
1 Emetic episode	16 (12%)	29 (20%)	
More than 1 emetic episode/rescued	35 (26%)	51 (36%)	
Nausea assessments: Number of patients	125	133	
No nausea over 24-h postoperative period	48 (38%)	42 (32%)	

230

231 The study populations in Table 6 consisted mainly of females undergoing laparoscopic
232 procedures.

233 In a placebo-controlled study conducted in 468 males undergoing outpatient procedures, a
234 single 4 mg I.V. ondansetron dose prevented postoperative vomiting over a 24-hour study period
235 in 79% of males receiving drug compared to 63% of males receiving placebo ($P<0.001$).

236 Two other placebo-controlled studies were conducted in 2,792 patients undergoing major
237 abdominal or gynecological surgeries to evaluate a single 4-mg or 8-mg I.V. ondansetron dose
238 for prevention of postoperative nausea and vomiting over a 24-hour study period. At the 4-mg
239 dosage, 59% of patients receiving ondansetron versus 45% receiving placebo in the first study

240 ($P<0.001$) and 41% of patients receiving ondansetron versus 30% receiving placebo in the second
 241 study ($P=0.001$) experienced no emetic episodes. No additional benefit was observed in patients
 242 who received I.V. ondansetron 8 mg compared to patients who received I.V. ondansetron 4 mg.

243 **Pediatric Studies:** Three double-blind, placebo-controlled studies have been performed
 244 (one US, two foreign) in 1,049 male and female patients (2 to 12 years of age) undergoing
 245 general anesthesia with nitrous oxide. The surgical procedures included tonsillectomy with or
 246 without adenoidectomy, strabismus surgery, herniorrhaphy, and orchidopexy. Patients were
 247 randomized to either single I.V. doses of ondansetron (0.1 mg/kg for pediatric patients weighing
 248 40 kg or less, 4 mg for pediatric patients weighing more than 40 kg) or placebo. Study drug was
 249 administered over at least 30 seconds, immediately prior to or following anesthesia induction.
 250 Ondansetron was significantly more effective than placebo in preventing nausea and vomiting.
 251 The results of these studies are summarized in Table 7.

252
 253

Table 7. Prevention of Postoperative Nausea and Vomiting in Pediatric Patients

Treatment Response Over 24 Hours	Ondansetron n (%)	Placebo n (%)	P Value
Study 1			
Number of patients	205	210	
0 Emetic episodes	140 (68%)	82 (39%)	≤ 0.001
Failure*	65 (32%)	128 (61%)	
Study 2			
Number of patients	112	110	
0 Emetic episodes	68 (61%)	38 (35%)	≤ 0.001
Failure*	44 (39%)	72 (65%)	
Study 3			
Number of patients	206	206	
0 Emetic episodes	123 (60%)	96 (47%)	≤ 0.01
Failure*	83 (40%)	110 (53%)	
Nausea assessments [†] :			
Number of patients	185	191	
None	119 (64%)	99 (52%)	≤ 0.01

254 * Failure was one or more emetic episodes, rescued, or withdrawn.

255 [†] Nausea measured as none, mild, or severe.

256

257 **Prevention of Further Postoperative Nausea and Vomiting:** Adult surgical patients
 258 receiving general balanced anesthesia (barbiturate: thiopental, methohexital, or thiamylal; opioid:
 259 alfentanil or fentanyl; nitrous oxide; neuromuscular blockade: succinylcholine/curare and/or

260 vecuronium or atracurium; and supplemental isoflurane) who received no prophylactic
 261 antiemetics and who experienced nausea and/or vomiting within 2 hours postoperatively were
 262 evaluated in two double-blind US studies involving 441 patients. Patients who experienced an
 263 episode of postoperative nausea and/or vomiting were given ZOFTRAN Injection (4 mg) I.V. over
 264 2 to 5 minutes, and this was significantly more effective than placebo. The results of these studies
 265 are summarized in Table 8.

266

267 **Table 8. Prevention of Further Postoperative Nausea and Vomiting in Adult Patients**

	Ondansetron 4 mg I.V.	Placebo	<i>P</i> Value
Study 1			
Emetic episodes: Number of patients	104	117	
Treatment response 24 h after study drug			
0 Emetic episodes	49 (47%)	19 (16%)	<0.001
1 Emetic episode	12 (12%)	9 (8%)	
More than 1 emetic episode/rescued	43 (41%)	89 (76%)	
Median time to first emetic episode (min)*	55.0	43.0	
Nausea assessments: Number of patients	98	102	
Mean nausea score over 24-h postoperative period [†]	1.7	3.1	
Study 2			
Emetic episodes: Number of patients	112	108	
Treatment response 24 h after study drug			
0 Emetic episodes	49 (44%)	28 (26%)	0.006
1 Emetic episode	14 (13%)	3 (3%)	
More than 1 emetic episode/rescued	49 (44%)	77 (71%)	
Median time to first emetic episode (min)*	60.5	34.0	
Nausea assessments: Number of patients	105	85	
Mean nausea score over 24-h postoperative period [†]	1.9	2.9	

268 * After administration of study drug.

269 [†] Nausea measured on a scale of 0-10 with 0 = no nausea, 10 = nausea as bad as it can be.

270

271 The study populations in Table 8 consisted mainly of women undergoing laparoscopic
272 procedures.

273 **Pediatric Studies:** One double-blind, placebo-controlled, US study was performed in 351
274 male and female outpatients (2 to 12 years of age) who received general anesthesia with nitrous
275 oxide and no prophylactic antiemetics. Surgical procedures were unrestricted. Patients who
276 experienced two or more emetic episodes within 2 hours following discontinuation of nitrous
277 oxide were randomized to either single I.V. doses of ondansetron (0.1 mg/kg for pediatric
278 patients weighing 40 kg or less, 4 mg for pediatric patients weighing more than 40 kg) or placebo
279 administered over at least 30 seconds. Ondansetron was significantly more effective than placebo
280 in preventing further episodes of nausea and vomiting. The results of the study are summarized
281 in Table 9.

282

283 **Table 9. Prevention of Further Postoperative Nausea and Vomiting in Pediatric Patients**

Treatment Response Over 24 Hours	Ondansetron n (%)	Placebo n (%)	P Value
Number of patients	180	171	≤0.001
0 Emetic episodes	96 (53%)	29 (17%)	
Failure*	84 (47%)	142 (83%)	

284 * Failure was one or more emetic episodes, rescued, or withdrawn.

285

286 **Repeat Dosing in Adults:** In patients who do not achieve adequate control of postoperative
287 nausea and vomiting following a single, prophylactic, preinduction, I.V. dose of ondansetron
288 4 mg, administration of a second I.V. dose of ondansetron 4 mg postoperatively does not provide
289 additional control of nausea and vomiting.

290 **INDICATIONS AND USAGE**

- 291 1. Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic
292 cancer chemotherapy, including high-dose cisplatin. Efficacy of the 32-mg single dose
293 beyond 24 hours in these patients has not been established.
- 294 2. Prevention of postoperative nausea and/or vomiting. As with other antiemetics, routine
295 prophylaxis is not recommended for patients in whom there is little expectation that nausea
296 and/or vomiting will occur postoperatively. In patients where nausea and/or vomiting must be
297 avoided postoperatively, ZOFTRAN Injection is recommended even where the incidence of
298 postoperative nausea and/or vomiting is low. For patients who do not receive prophylactic
299 ZOFTRAN Injection and experience nausea and/or vomiting postoperatively, ZOFTRAN
300 Injection may be given to prevent further episodes (see CLINICAL TRIALS).

301 **CONTRAINDICATIONS**

302 ZOFTRAN Injection and ZOFTRAN Injection Premixed are contraindicated for patients known
303 to have hypersensitivity to the drug.

304 **WARNINGS**

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

307 **PRECAUTIONS**

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

312 **Drug Interactions:** Ondansetron does not itself appear to induce or inhibit the cytochrome
313 P-450 drug-metabolizing enzyme system of the liver. Because ondansetron is metabolized by
314 hepatic cytochrome P-450 drug-metabolizing enzymes, inducers or inhibitors of these enzymes
315 may change the clearance and, hence, the half-life of ondansetron. On the basis of limited
316 available data, no dosage adjustment is recommended for patients on these drugs. Tumor
317 response to chemotherapy in the P 388 mouse leukemia model is not affected by ondansetron. In
318 humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.

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

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

326 **Pregnancy: Teratogenic Effects:** Pregnancy Category B. Reproduction studies have been
327 performed in pregnant rats and rabbits at I.V. doses up to 4 mg/kg per day and have revealed no
328 evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, no
329 adequate and well-controlled studies in pregnant women. Because animal reproduction studies
330 are not always predictive of human response, this drug should be used during pregnancy only if
331 clearly needed.

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

335 **Pediatric Use:** Little information is available about dosage in pediatric patients under 2 years
336 of age (see DOSAGE AND ADMINISTRATION section for use in pediatric patients 4 to
337 18 years of age receiving cancer chemotherapy or for use in pediatric patients 2 to 12 years of age
338 receiving general anesthesia).

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, 862 were 65
 341 years of age and over. No overall differences in safety or effectiveness were observed between
 342 these subjects and younger subjects, and other reported clinical experience has not identified
 343 differences in responses between the elderly and younger patients, but greater sensitivity of some
 344 older individuals cannot be ruled out. Dosage adjustment is not needed in patients over the age of
 345 65 (see CLINICAL PHARMACOLOGY).

346 **ADVERSE REACTIONS**

347 **Chemotherapy-Induced Nausea and Vomiting:** The adverse events in Table 10 have been
 348 reported in individuals receiving ondansetron at a dosage of three 0.15-mg/kg doses or as a single
 349 32-mg dose in clinical trials. These patients were receiving concomitant chemotherapy, primarily
 350 cisplatin, and I.V. fluids. Most were receiving a diuretic.

351

352 **Table 10. Principal Adverse Events in Comparative Trials**

	Number of Patients With Event			
	ZOFTRAN Injection 0.15 mg/kg x 3 n = 419	ZOFTRAN Injection 32 mg x 1 n = 220	Metoclopramide n = 156	Placebo n = 34
Diarrhea	16%	8%	44%	18%
Headache	17%	25%	7%	15%
Fever	8%	7%	5%	3%
Akathisia	0%	0%	6%	0%
Acute dystonic reactions*	0%	0%	5%	0%

353 * See Neurological.

354

355 The following have been reported during controlled clinical trials:

356 **Cardiovascular:** Rare cases of angina (chest pain), electrocardiographic alterations,
 357 hypotension, and tachycardia have been reported. In many cases, the relationship to ZOFTRAN
 358 Injection was unclear.

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

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

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

368 **Neurological:** There have been rare reports consistent with, but not diagnostic of,
 369 extrapyramidal reactions in patients receiving ZOFRAN Injection, and rare cases of grand mal
 370 seizure. The relationship to ZOFRAN was unclear.

371 **Other:** Rare cases of hypokalemia have been reported. The relationship to ZOFRAN Injection
 372 was unclear.

373 **Postoperative Nausea and Vomiting:** The adverse events in Table 11 have been reported in
 374 $\geq 2\%$ of adults receiving ondansetron at a dosage of 4 mg I.V. over 2 to 5 minutes in clinical
 375 trials. Rates of these events were not significantly different in the ondansetron and placebo
 376 groups. These patients were receiving multiple concomitant perioperative and postoperative
 377 medications.

378
 379 **Table 11. Adverse Events in $\geq 2\%$ of Adults Receiving Ondansetron at a Dosage of 4 mg I.V.**
 380 **over 2 to 5 Minutes in Clinical Trials**

	ZOFRAN Injection 4 mg I.V. n = 547 patients	Placebo n = 547 patients
Headache	92 (17%)	77 (14%)
Dizziness	67 (12%)	88 (16%)
Musculoskeletal pain	57 (10%)	59 (11%)
Drowsiness/sedation	44 (8%)	37 (7%)
Shivers	38 (7%)	39 (7%)
Malaise/fatigue	25 (5%)	30 (5%)
Injection site reaction	21 (4%)	18 (3%)
Urinary retention	17 (3%)	15 (3%)
Postoperative CO ₂ -related pain*	12 (2%)	16 (3%)
Chest pain (unspecified)	12 (2%)	15 (3%)
Anxiety/agitation	11 (2%)	16 (3%)
Dysuria	11 (2%)	9 (2%)
Hypotension	10 (2%)	12 (2%)
Fever	10 (2%)	6 (1%)
Cold sensation	9 (2%)	8 (1%)
Pruritus	9 (2%)	3 (<1%)
Paresthesia	9 (2%)	2 (<1%)

381 * Sites of pain included abdomen, stomach, joints, rib cage, shoulder.

382
 383 **Pediatric Use:** The adverse events in Table 12 were the most commonly reported adverse
 384 events in pediatric patients receiving ondansetron (a single 0.1-mg/kg dose for pediatric patients
 385 weighing 40 kg or less, or 4 mg for pediatric patients weighing more than 40 kg) administered
 386 intravenously over at least 30 seconds. Rates of these events were not significantly different in

387 the ondansetron and placebo groups. These patients were receiving multiple concomitant
388 perioperative and postoperative medications.

389

390 **Table 12. Frequency of Adverse Events From Controlled Studies in Pediatric Patients**

Adverse Event	Ondansetron n = 755 Patients	Placebo n = 731 Patients
Wound problem	80 (11%)	86 (12%)
Anxiety/agitation	49 (6%)	47 (6%)
Headache	44 (6%)	43 (6%)
Drowsiness/sedation	41 (5%)	56 (8%)
Pyrexia	32 (4%)	41 (6%)

391

392 **Observed During Clinical Practice:** In addition to adverse events reported from clinical
393 trials, the following events have been identified during post-approval use of intravenous
394 formulations of ZOFRAN. Because they are reported voluntarily from a population of unknown
395 size, estimates of frequency cannot be made. The events have been chosen for inclusion due to a
396 combination of their seriousness, frequency of reporting, or potential causal connection to
397 ZOFRAN.

398 **Cardiovascular:** Arrhythmias (including ventricular and supraventricular tachycardia,
399 premature ventricular contractions, and atrial fibrillation), bradycardia, electrocardiographic
400 alterations (including second-degree heart block and ST segment depression), palpitations, and
401 syncope.

402 **General:** Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g.,
403 anaphylaxis/anaphylactoid reactions, angioedema, bronchospasm, cardiopulmonary arrest,
404 hypotension, laryngeal edema, laryngospasm, shock, shortness of breath, stridor) have also been
405 reported.

406 **Hepatobiliary:** Liver enzyme abnormalities have been reported. Liver failure and death have
407 been reported in patients with cancer receiving concurrent medications including potentially
408 hepatotoxic cytotoxic chemotherapy and antibiotics. The etiology of the liver failure is unclear.

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

410 **Lower Respiratory:** Hiccups

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

412 **Skin:** Urticaria

413 **Special Senses:** Transient blurred vision, in some cases associated with abnormalities of
414 accommodation, and transient dizziness during or shortly after I.V. infusion.

415 **DRUG ABUSE AND DEPENDENCE**

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

418 **OVERDOSAGE**

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

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

430 **DOSAGE AND ADMINISTRATION**

431 **Prevention of Chemotherapy-Induced Nausea and Vomiting:** The recommended I.V.
432 dosage of ZOFTRAN is a single 32-mg dose or three 0.15-mg/kg doses. A single 32-mg dose is
433 infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy. The
434 recommended infusion rate should not be exceeded (see OVERDOSAGE). With the three-dose
435 (0.15-mg/kg) regimen, the first dose is infused over 15 minutes beginning 30 minutes before the
436 start of emetogenic chemotherapy. Subsequent doses (0.15 mg/kg) are administered 4 and
437 8 hours after the first dose of ZOFTRAN.

438 ZOFTRAN Injection should not be mixed with solutions for which physical and chemical
439 compatibility have not been established. In particular, this applies to alkaline solutions as a
440 precipitate may form.

441 **Vial: DILUTE BEFORE USE.** ZOFTRAN Injection should be diluted in 50 mL of 5%
442 Dextrose Injection or 0.9% Sodium Chloride Injection before administration.

443 **Flexible Plastic Container:** ZOFTRAN Injection Premixed, 32 mg in 5% Dextrose, 50 mL,
444 **REQUIRES NO DILUTION.**

445 **Pediatric Use:** On the basis of the limited available information (see CLINICAL TRIALS:
446 Pediatric Studies and CLINICAL PHARMACOLOGY: Pharmacokinetics), the dosage in
447 pediatric patients 4 to 18 years of age should be three 0.15-mg/kg doses (see above). Little
448 information is available about dosage in pediatric patients 3 years of age and younger.

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

450 **Prevention of Postoperative Nausea and Vomiting:** The recommended I.V. dosage of
451 ZOFTRAN for adults is 4 mg **undiluted** administered intravenously in not less than 30 seconds,
452 preferably over 2 to 5 minutes, immediately before induction of anesthesia, or postoperatively if
453 the patient experiences nausea and/or vomiting occurring shortly after surgery. Alternatively,
454 4 mg **undiluted** may be administered intramuscularly as a single injection for adults. While
455 recommended as a fixed dose for patients weighing more than 40 kg, few patients above 80 kg
456 have been studied. In patients who do not achieve adequate control of postoperative nausea and

457 vomiting following a single, prophylactic, preinduction, I.V. dose of ondansetron 4 mg,
458 administration of a second I.V. dose of 4 mg ondansetron postoperatively does not provide
459 additional control of nausea and vomiting.

460 **Vial:** ZOFRAN Injection **REQUIRES NO DILUTION FOR ADMINISTRATION FOR**
461 **POSTOPERATIVE NAUSEA AND VOMITING.**

462 **Pediatric Use:** The recommended I.V. dosage of ZOFRAN for pediatric patients (2 to
463 12 years of age) is a single 0.1-mg/kg dose for pediatric patients weighing 40 kg or less, or a
464 single 4-mg dose for pediatric patients weighing more than 40 kg. The rate of administration
465 should not be less than 30 seconds, preferably over 2 to 5 minutes. Little information is available
466 about dosage in pediatric patients younger than 2 years of age.

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

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

471 **Dosage Adjustment for Patients With Impaired Hepatic Function:** In patients with
472 severe hepatic impairment (Child-Pugh¹ score of 10 or greater), a single maximal daily dose of
473 8 mg to be infused over 15 minutes beginning 30 minutes before the start of the emetogenic
474 chemotherapy is recommended. There is no experience beyond first-day administration of
475 ondansetron.

476 **ZOFRAN Injection Premixed in Flexible Plastic Containers: Instructions for Use:**

477 **To Open:** Tear outer wrap at notch and remove solution container. Check for minute leaks by
478 squeezing container firmly. If leaks are found, discard unit as sterility may be impaired.

479 **Preparation for Administration:** Use aseptic technique.

- 480 1. Close flow control clamp of administration set.
- 481 2. Remove cover from outlet port at bottom of container.
- 482 3. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly
483 seated. NOTE: See full directions on administration set carton.
- 484 4. Suspend container from hanger.
- 485 5. Squeeze and release drip chamber to establish proper fluid level in chamber during infusion
486 of ZOFRAN Injection Premixed.
- 487 6. Open flow control clamp to expel air from set. Close clamp.
- 488 7. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
- 489 8. Perform venipuncture.
- 490 9. Regulate rate of administration with flow control clamp.

491 **Caution:** ZOFRAN Injection Premixed in flexible plastic containers is to be administered by
492 I.V. drip infusion only. ZOFRAN Injection Premixed should not be mixed with solutions for
493 which physical and chemical compatibility have not been established. In particular, this applies
494 to alkaline solutions as a precipitate may form. If used with a primary I.V. fluid system, the
495 primary solution should be discontinued during ZOFRAN Injection Premixed infusion.

496 Do not administer unless solution is clear and container is undamaged.

497 **Warning:** Do not use flexible plastic container in series connections.
498 **Stability:** ZOFRAN Injection is stable at room temperature under normal lighting conditions for
499 48 hours after dilution with the following I.V. fluids: 0.9% Sodium Chloride Injection, 5%
500 Dextrose Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, 5% Dextrose and 0.45%
501 Sodium Chloride Injection, and 3% Sodium Chloride Injection.

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

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

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

510 HOW SUPPLIED

511 **ZOFRAN Injection**, 2 mg/mL, is supplied as follows:

512 NDC 0173-0442-02 2-mL single-dose vials (Carton of 5)

513 NDC 0173-0442-00 20-mL multidose vials (Singles)

514 **Store between 2° and 30°C (36° and 86°F). Protect from light.**

515 **ZOFRAN Injection Premixed**, 32 mg/50 mL, in 5% Dextrose, contains no preservatives and
516 is supplied as a sterile, premixed solution for I.V. administration in single-dose, flexible plastic
517 containers (NDC 0173-0461-00) (case of 6).

518 **Store between 2° and 30°C (36° and 86°F). Protect from light. Avoid excessive heat.**

519 **Protect from freezing.**

520 REFERENCE

521 1. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the
522 oesophagus for bleeding oesophageal varices. *Brit J Surg.* 1973;60:646-649.

523



524

525 GlaxoSmithKline

526 Research Triangle Park, NC 27709

527

528 ZOFRAN[®] Injection Premixed:

529 Manufactured for GlaxoSmithKline

530 Research Triangle Park, NC 27709

531 by Abbott Laboratories, North Chicago, IL 60064

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