

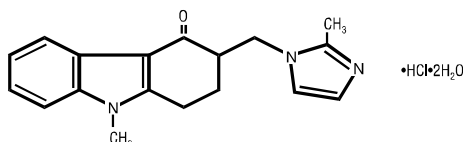
1 PRESCRIBING INFORMATION

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 CYP3A4 inducers, carbamazepine, or phenytoin, reduction in AUC, C_{max} , and $T_{1/2}$
84 of ondansetron was observed.¹ This resulted in a significant increase in clearance. However, on
85 the basis of available data, no dosage adjustment for ondansetron is recommended (see
86 PRECAUTIONS: [Drug Interactions](#)).

87 In humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of
88 ondansetron.

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

91

92 **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

93

94 A reduction in clearance and increase in elimination half-life are seen in patients over 75 years
95 of age. In clinical trials with cancer patients, safety and efficacy were similar in patients over 65
96 years of age and those under 65 years of age; there was an insufficient number of patients over
97 75 years of age to permit conclusions in that age-group. No dosage adjustment is recommended
98 in the elderly.

99 In patients with mild-to-moderate hepatic impairment, clearance is reduced twofold and mean
100 half-life is increased to 11.6 hours compared to 5.7 hours in normals. In patients with severe
101 hepatic impairment (Child-Pugh score² of 10 or greater), clearance is reduced twofold to threefold
102 and apparent volume of distribution is increased with a resultant increase in half-life to 20 hours.
103 In patients with severe hepatic impairment, a total daily dose of 8 mg should not be exceeded.

104 Due to the very small contribution (5%) of renal clearance to the overall clearance, renal
105 impairment was not expected to significantly influence the total clearance of ondansetron.

106 However, ondansetron mean plasma clearance was reduced by about 41% in patients with severe
107 renal impairment (creatinine clearance <30 mL/min). This reduction in clearance is variable and
108 was not consistent with an increase in half-life. No reduction in dose or dosing frequency in
109 these patients is warranted.

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

120 In a study of 21 pediatric patients (aged 3 to 12 years) who were undergoing surgery requiring
121 anesthesia for a duration of 45 minutes to 2 hours, a single I.V. dose of ondansetron, 2 mg (3 to
122 7 years) or 4 mg (8 to 12 years), was administered immediately prior to anesthesia induction.
123 Mean weight-normalized clearance and volume of distribution values in these pediatric surgical
124 patients were similar to those previously reported for young adults. Mean terminal half-life was
125 slightly reduced in pediatric patients (range, 2.5 to 3 hours) in comparison with adults (range, 3 to
126 3.5 hours).

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

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

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

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

145 **CLINICAL TRIALS**

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

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

155
 156 **Table 2. Prevention of Chemotherapy-Induced Nausea and Emesis in Single-Day Cisplatin**
 157 **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

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

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

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

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

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

168

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

176
 177 **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

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

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

182

183 In a stratified, randomized, double-blind, parallel-group, multicenter study, a single 32-mg
 184 dose of ondansetron was compared with three 0.15-mg/kg doses in patients receiving cisplatin
 185 doses of either 50 to 70 mg/m² or ≥ 100 mg/m². Patients received the first ondansetron dose
 186 30 minutes before cisplatin. Two additional ondansetron doses were administered 4 and 8 hours

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

189

190 **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

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

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

193

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

198

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

	ZOFTRAN Injection	Placebo	P 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

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

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

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

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

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

208

209 **Re-treatment:** In uncontrolled trials, 127 patients receiving cisplatin (median dose,
 210 100 mg/m²) and ondansetron who had two or fewer emetic episodes were re-treated with
 211 ondansetron and chemotherapy, mainly cisplatin, for a total of 269 re-treatment courses (median,
 212 2; range, 1 to 10). No emetic episodes occurred in 160 (59%), and two or fewer emetic episodes
 213 occurred in 217 (81%) re-treatment courses.

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

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

224 **Postoperative Nausea and Vomiting: *Prevention of Postoperative Nausea and***
225 ***Vomiting:*** Adult surgical patients who received ondansetron immediately before the induction
226 of general balanced anesthesia (barbiturate: thiopental, methohexital, or thiamylal; opioid:
227 alfentanil or fentanyl; nitrous oxide; neuromuscular blockade: succinylcholine/curare and/or
228 vecuronium or atracurium; and supplemental isoflurane) were evaluated in two double-blind US
229 studies involving 554 patients. ZOFTRAN Injection (4 mg) I.V. given over 2 to 5 minutes was
230 significantly more effective than placebo. The results of these studies are summarized in [Table 6](#).
231

232 **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%)	

233
 234 The study populations in Table 6 consisted mainly of females undergoing laparoscopic
 235 procedures.
 236 In a placebo-controlled study conducted in 468 males undergoing outpatient procedures, a
 237 single 4 mg I.V. ondansetron dose prevented postoperative vomiting over a 24-hour study period
 238 in 79% of males receiving drug compared to 63% of males receiving placebo ($P < 0.001$).
 239 Two other placebo-controlled studies were conducted in 2,792 patients undergoing major
 240 abdominal or gynecological surgeries to evaluate a single 4-mg or 8-mg I.V. ondansetron dose
 241 for prevention of postoperative nausea and vomiting over a 24-hour study period. At the 4-mg
 242 dosage, 59% of patients receiving ondansetron versus 45% receiving placebo in the first study

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

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

255
 256

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

Treatment Response Over 24 Hours	Ondansetron n (%)	Placebo n (%)	<i>P</i> 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

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

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

259

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

263 vecuronium or atracurium; and supplemental isoflurane) who received no prophylactic
 264 antiemetics and who experienced nausea and/or vomiting within 2 hours postoperatively were
 265 evaluated in two double-blind US studies involving 441 patients. Patients who experienced an
 266 episode of postoperative nausea and/or vomiting were given ZOFTRAN Injection (4 mg) I.V. over
 267 2 to 5 minutes, and this was significantly more effective than placebo. The results of these studies
 268 are summarized in Table 8.

269

270 **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	

271 * After administration of study drug.

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

273

274 The study populations in [Table 8](#) consisted mainly of women undergoing laparoscopic
275 procedures.

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

285

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

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

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

288

289 **Repeat Dosing in Adults:** In patients who do not achieve adequate control of postoperative
290 nausea and vomiting following a single, prophylactic, preinduction, I.V. dose of ondansetron
291 4 mg, administration of a second I.V. dose of ondansetron 4 mg postoperatively does not provide
292 additional control of nausea and vomiting.

293 **INDICATIONS AND USAGE**

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

304 **CONTRAINDICATIONS**

305 ZOFTRAN Injection and ZOFTRAN Injection Premixed are contraindicated for patients known
306 to have hypersensitivity to the drug.

307 **WARNINGS**

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

310 **PRECAUTIONS**

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

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

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

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

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

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

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

339 **Pregnancy: Teratogenic Effects:** Pregnancy Category B. Reproduction studies have been
340 performed in pregnant rats and rabbits at I.V. doses up to 4 mg/kg per day and have revealed no
341 evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, no
342 adequate and well-controlled studies in pregnant women. Because animal reproduction studies

343 are not always predictive of human response, this drug should be used during pregnancy only if
344 clearly needed.

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

348 **Pediatric Use:** Little information is available about dosage in pediatric patients under 2 years
349 of age (see [DOSAGE AND ADMINISTRATION](#) section for use in pediatric patients 4 to
350 18 years of age receiving cancer chemotherapy or for use in pediatric patients 2 to 12 years of age
351 receiving general anesthesia).

352 **Geriatric Use:** Of the total number of subjects enrolled in cancer chemotherapy-induced and
353 postoperative nausea and vomiting in US- and foreign-controlled clinical trials, 862 were 65
354 years of age and over. No overall differences in safety or effectiveness were observed between
355 these subjects and younger subjects, and other reported clinical experience has not identified
356 differences in responses between the elderly and younger patients, but greater sensitivity of some
357 older individuals cannot be ruled out. Dosage adjustment is not needed in patients over the age of
358 65 (see [CLINICAL PHARMACOLOGY](#)).

359 **ADVERSE REACTIONS**

360 **Chemotherapy-Induced Nausea and Vomiting:** The adverse events in Table 10 have been
361 reported in individuals receiving ondansetron at a dosage of three 0.15-mg/kg doses or as a single
362 32-mg dose in clinical trials. These patients were receiving concomitant chemotherapy, primarily
363 cisplatin, and I.V. fluids. Most were receiving a diuretic.

364

365 **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%

366 * See [Neurological](#).

367

368 The following have been reported during controlled clinical trials:

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

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

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

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

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

384 **Other:** Rare cases of hypokalemia have been reported. The relationship to ZOFTRAN Injection
385 was unclear.

386 **Postoperative Nausea and Vomiting:** The adverse events in [Table 11](#) have been reported in
387 $\geq 2\%$ of adults receiving ondansetron at a dosage of 4 mg I.V. over 2 to 5 minutes in clinical
388 trials. Rates of these events were not significantly different in the ondansetron and placebo
389 groups. These patients were receiving multiple concomitant perioperative and postoperative
390 medications.

391

392 **Table 11. Adverse Events in $\geq 2\%$ of Adults Receiving Ondansetron at a Dosage of 4 mg I.V.**
 393 **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%)

394 * Sites of pain included abdomen, stomach, joints, rib cage, shoulder.
 395

396 **Pediatric Use:** The adverse events in [Table 12](#) were the most commonly reported adverse
 397 events in pediatric patients receiving ondansetron (a single 0.1-mg/kg dose for pediatric patients
 398 weighing 40 kg or less, or 4 mg for pediatric patients weighing more than 40 kg) administered
 399 intravenously over at least 30 seconds. Rates of these events were not significantly different in
 400 the ondansetron and placebo groups. These patients were receiving multiple concomitant
 401 perioperative and postoperative medications.
 402

403 **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%)

404
 405 **Observed During Clinical Practice:** In addition to adverse events reported from clinical
 406 trials, the following events have been identified during post-approval use of intravenous
 407 formulations of ZOFTRAN. Because they are reported voluntarily from a population of unknown
 408 size, estimates of frequency cannot be made. The events have been chosen for inclusion due to a
 409 combination of their seriousness, frequency of reporting, or potential causal connection to
 410 ZOFTRAN.

411 **Cardiovascular:** Arrhythmias (including ventricular and supraventricular tachycardia,
 412 premature ventricular contractions, and atrial fibrillation), bradycardia, electrocardiographic
 413 alterations (including second-degree heart block and ST segment depression), palpitations, and
 414 syncope.

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

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

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

423 **Lower Respiratory:** Hiccups

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

425 **Skin:** Urticaria

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

428 **DRUG ABUSE AND DEPENDENCE**

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

431 **OVERDOSAGE**

432 There is no specific antidote for ondansetron overdose. Patients should be managed with
 433 appropriate supportive therapy. Individual doses as large as 150 mg and total daily dosages

434 (three doses) as large as 252 mg have been administered intravenously without significant
435 adverse events. These doses are more than 10 times the recommended daily dose.

436 In addition to the adverse events listed above, the following events have been described in the
437 setting of ondansetron overdose: "Sudden blindness" (amaurosis) of 2 to 3 minutes' duration plus
438 severe constipation occurred in one patient that was administered 72 mg of ondansetron
439 intravenously as a single dose. Hypotension (and faintness) occurred in another patient that took
440 48 mg of oral ondansetron. Following infusion of 32 mg over only a 4-minute period, a
441 vasovagal episode with transient second-degree heart block was observed. In all instances, the
442 events resolved completely.

443 **DOSAGE AND ADMINISTRATION**

444 **Prevention of Chemotherapy-Induced Nausea and Vomiting:** The recommended I.V.
445 dosage of ZOFTRAN is a single 32-mg dose or three 0.15-mg/kg doses. A single 32-mg dose is
446 infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy. The
447 recommended infusion rate should not be exceeded (see [OVERDOSAGE](#)). With the three-dose
448 (0.15-mg/kg) regimen, the first dose is infused over 15 minutes beginning 30 minutes before the
449 start of emetogenic chemotherapy. Subsequent doses (0.15 mg/kg) are administered 4 and
450 8 hours after the first dose of ZOFTRAN.

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

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

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

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

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

463 **Prevention of Postoperative Nausea and Vomiting:** The recommended I.V. dosage of
464 ZOFTRAN for adults is 4 mg **undiluted** administered intravenously in not less than 30 seconds,
465 preferably over 2 to 5 minutes, immediately before induction of anesthesia, or postoperatively if
466 the patient experiences nausea and/or vomiting occurring shortly after surgery. Alternatively,
467 4 mg **undiluted** may be administered intramuscularly as a single injection for adults. While
468 recommended as a fixed dose for patients weighing more than 40 kg, few patients above 80 kg
469 have been studied. In patients who do not achieve adequate control of postoperative nausea and
470 vomiting following a single, prophylactic, preinduction, I.V. dose of ondansetron 4 mg,
471 administration of a second I.V. dose of 4 mg ondansetron postoperatively does not provide
472 additional control of nausea and vomiting.

473 **Vial:** ZOFTRAN Injection **REQUIRES NO DILUTION FOR ADMINISTRATION FOR**
474 **POSTOPERATIVE NAUSEA AND VOMITING.**

475 **Pediatric Use:** The recommended I.V. dosage of ZOFTRAN for pediatric patients (2 to
476 12 years of age) is a single 0.1-mg/kg dose for pediatric patients weighing 40 kg or less, or a
477 single 4-mg dose for pediatric patients weighing more than 40 kg. The rate of administration
478 should not be less than 30 seconds, preferably over 2 to 5 minutes. Little information is available
479 about dosage in pediatric patients younger than 2 years of age.

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

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

484 **Dosage Adjustment for Patients With Impaired Hepatic Function:** In patients with
485 severe hepatic impairment (Child-Pugh² score of 10 or greater), a single maximal daily dose of
486 8 mg to be infused over 15 minutes beginning 30 minutes before the start of the emetogenic
487 chemotherapy is recommended. There is no experience beyond first-day administration of
488 ondansetron.

489 **ZOFTRAN Injection Premixed in Flexible Plastic Containers: Instructions for Use:**

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

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

- 493 1. Close flow control clamp of administration set.
- 494 2. Remove cover from outlet port at bottom of container.
- 495 3. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly
496 seated. NOTE: See full directions on administration set carton.
- 497 4. Suspend container from hanger.
- 498 5. Squeeze and release drip chamber to establish proper fluid level in chamber during infusion
499 of ZOFTRAN Injection Premixed.
- 500 6. Open flow control clamp to expel air from set. Close clamp.
- 501 7. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
- 502 8. Perform venipuncture.
- 503 9. Regulate rate of administration with flow control clamp.

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

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

510 **Warning:** Do not use flexible plastic container in series connections.

511 **Stability:** ZOFTRAN Injection is stable at room temperature under normal lighting conditions for
512 48 hours after dilution with the following I.V. fluids: 0.9% Sodium Chloride Injection, 5%

513 Dextrose Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, 5% Dextrose and 0.45%
514 Sodium Chloride Injection, and 3% Sodium Chloride Injection.

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

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

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

523 HOW SUPPLIED

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

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

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

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

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

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

532 **Protect from freezing.**

533 REFERENCE

- 534 1. Britto MR, Hussey EK, Mydlow P, et al. Effect of enzyme inducers on ondansetron (OND)
535 metabolism in humans. *Clin Pharmacol Ther* 1997;61:228.
- 536 2. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the
537 oesophagus for bleeding oesophageal varices. *Brit J Surg*. 1973;60:646-649.
- 538 3. Villikka K, Kivisto KT, Neuvonen PJ. The effect of rifampin on the pharmacokinetics of oral
539 and intravenous ondansetron. *Clin Pharmacol Ther* 1999;65:377-381.
- 540 4. De Witte JL, Schoenmaekers B, Sessler DI, et al. *Anesth Analg* 2001;92:1319-1321.
- 541 5. Arcioni R, della Rocca M, Romanò R, et al. *Anesth Analg* 2002;94:1553-1557.
- 542



543
544 GlaxoSmithKline
545 Research Triangle Park, NC 27709

546
547 ZOFRAN[®] Injection Premixed:
548 Manufactured for GlaxoSmithKline
549 Research Triangle Park, NC 27709

550 by Abbott Laboratories, North Chicago, IL 60064

551

552 ©2004, GlaxoSmithKline. All rights reserved.

553

554 May 2004

RL-2083