

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-103/S-017

20-605/S-004

20-781/S-001

Trade Name: Zofran Tablets, Zofran Oral Solution and Zofran Orally Disintegrating Tablets

Generic Name: (ondansetron)

Sponsor: Glaxo Wellcome, Inc.

Approval Date: April 11, 2000

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**CENTER FOR DRUG EVALUATION AND
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APPROVAL LETTER

NDA 20-103/S-017
NDA 20-605/S-004
NDA 20-781/S-001

Glaxo Wellcome, Inc.
Attention: Craig A. Metz, Ph.D.
Director, Regulatory Affairs
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Dr. Metz:

Please refer to your supplemental new drug applications dated October 13, 1999, received October 14, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zofran (ondansetron) Tablets, Oral Solution, and Zofran ODT Orally-Disintegrating Tablets, respectively.

These supplemental new drug applications provide for the following revisions to the package insert:

1. A new subsection, entitled "Observed During Clinical Practice," within the ADVERSE REACTIONS section,
2. Addition of several new adverse reactions in the Observed During Clinical Practice subsection, and
3. Revisions to the OVERDOSAGE section to provide consistency in wording between the oral and injectable product package inserts.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted final printed labeling (package insert submitted October 13, 1999). Accordingly, these supplemental applications are approved effective on the date of this letter.

At the next printing of the package insert, please revise all instances of the word "_____to" to "pediatric patients" in accordance with 21 CFR 201.57(f)(9). The Division may be informed of this revision in the subsequent annual reports.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that

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you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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cc:

Archival NDAs 20-103, 20-605, 20-781

HFD-180/Div. Files

HFD-180/M.McNeil

HF-2/MedWatch (with labeling)

HFD-002/ORM (with labeling)

HFD-103/ADRA (with labeling)

HFD-40/DDMAC (with labeling)

HFI-20/Press Office (with labeling)

HFD-400/OPDRA (with labeling)

HFD-613/OGD (with labeling)

HFD-095/DDMS-IMT (with labeling)

HFD-820/DNDC Division Director

DISTRICT OFFICE

Drafted by: mm/April 7, 2000

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APPROVAL (AP)

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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LABELING

1 PRESCRIBING INFORMATION

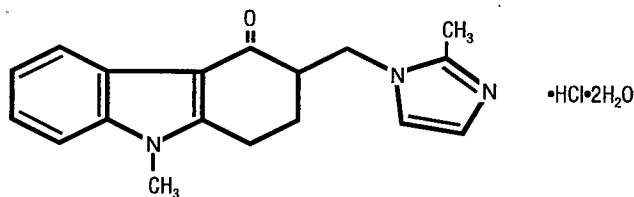
2 **ZOFRAN[®]**
3 **(ondansetron hydrochloride)**
4 **Tablets**

5
6 **ZOFRAN ODT[®]**
7 **(ondansetron)**
8 **Orally Disintegrating Tablets**

9
10 **ZOFRAN[®]**
11 **(ondansetron hydrochloride)**
12 **Oral Solution**

13 **DESCRIPTION**

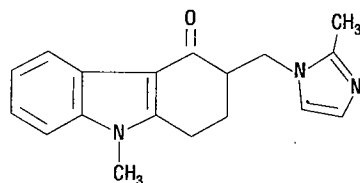
14 The active ingredient in ZOFRAN Tablets and ZOFRAN Oral Solution is ondansetron
15 hydrochloride (HCl) as the dihydrate, the racemic form of ondansetron and a selective blocking
16 agent of the serotonin 5-HT₃ receptor type. Chemically it is (±) 1, 2, 3, 9-tetrahydro-9-methyl-3-
17 [(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, monohydrochloride, dihydrate. It has
18 the following structural formula:



20
21
22 The empirical formula is C₁₈H₁₉N₃O·HCl·2H₂O, representing a molecular weight of 365.9.

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

25 The active ingredient in ZOFRAN ODT Orally Disintegrating Tablets is ondansetron base, the
26 racemic form of ondansetron, and a selective blocking agent of the serotonin 5-HT₃ receptor type.
27 Chemically it is (±) 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-
28 carbazol-4-one. It has the following structural formula:



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

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

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

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

49 **CLINICAL PHARMACOLOGY**

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

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

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

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

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

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

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

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

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

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

102

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

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

104

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

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

106

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

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

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

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

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

129 **CLINICAL TRIALS**

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

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

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

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

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

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

155

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

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

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

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

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

163

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

169

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

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

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

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

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

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

179

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

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

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

202 **Single High-Dose Fraction Radiotherapy:** Ondansetron was significantly more effective
203 than metoclopramide with respect to complete control of emesis (0 emetic episodes) in a
204 double-blind trial in 105 patients receiving single high-dose radiotherapy (800 to 1,000 cGy) over
205 an anterior or posterior field size of ≥ 80 cm² to the abdomen. Patients received the first dose of
206 ZOFTRAN Tablets (8 mg) or metoclopramide (10 mg) 1 to 2 hours before radiotherapy. If
207 radiotherapy was given in the morning, 2 additional doses of study treatment were given (1 tablet
208 late afternoon and 1 tablet before bedtime). If radiotherapy was given in the afternoon, patients
209 took only 1 further tablet that day before bedtime. Patients continued the oral medication on a
210 3 times a day basis for 3 days.

211 **Daily Fractionated Radiotherapy:** Ondansetron was significantly more effective than
212 prochlorperazine with respect to complete control of emesis (0 emetic episodes) in a double-blind
213 trial in 135 patients receiving a 1- to 4-week course of fractionated radiotherapy (180 cGy doses)
214 over a field size of ≥ 100 cm² to the abdomen. Patients received the first dose of ZOFTRAN Tablets
215 (8 mg) or prochlorperazine (10 mg) 1 to 2 hours before the patient received the first daily
216 radiotherapy fraction, with 2 subsequent doses on a 3 times a day basis. Patients continued the oral
217 medication on a 3 times a day basis on each day of radiotherapy.

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

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

228 **INDICATIONS AND USAGE**

- 229 1. Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy,
230 including cisplatin ≥ 50 mg/m².
- 231 2. Prevention of nausea and vomiting associated with initial and repeat courses of moderately
232 emetogenic cancer chemotherapy.

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

242 **CONTRAINDICATIONS**

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

245 **WARNINGS**

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

248 **PRECAUTIONS**

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

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

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

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

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

271 basis of available data, no dosage adjustment for ondansetron is recommended for patients on
272 these drugs.^{1,3}

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

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

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

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

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

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

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

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

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

307 **ADVERSE REACTIONS**

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

311 **Chemotherapy-Induced Nausea and Vomiting:** The adverse events in Table 5 have been
 312 reported in $\geq 5\%$ of adult patients receiving a single 24-mg ZOFTRAN Tablet in 2 trials. These
 313 patients were receiving concurrent highly emetogenic cisplatin-based chemotherapy regimens
 314 (cisplatin dose ≥ 50 mg/m²).

315
 316 **Table 5. Principal Adverse Events in US Trials: Single Day Therapy With 24-mg ZOFTRAN**
 317 **Tablets (Highly Emetogenic Chemotherapy)**

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

318
 319 The adverse events in Table 6 have been reported in $\geq 5\%$ of adults receiving either 8 mg of
 320 ZOFTRAN Tablets 2 or 3 times a day for 3 days or placebo in 4 trials. These patients were
 321 receiving concurrent moderately emetogenic chemotherapy, primarily cyclophosphamide-based
 322 regimens.

323
 324 **Table 6. Principal Adverse Events in US Trials: 3 Days of Therapy With 8-mg ZOFTRAN**
 325 **Tablets (Moderately Emetogenic Chemotherapy)**

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

326
 327 **Central Nervous System:** There have been rare reports consistent with, but not diagnostic
 328 of, extrapyramidal reactions in patients receiving ondansetron.

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

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

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

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

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

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

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

353

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

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

356

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

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

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

370 **Hepatobiliary:** Liver enzyme abnormalities

371 **Lower Respiratory:** Hiccups

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

373 **Skin:** Urticaria

374 **DRUG ABUSE AND DEPENDENCE**

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

377 **OVERDOSAGE**

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

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

389 **DOSAGE AND ADMINISTRATION**

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

395 **Prevention of Nausea and Vomiting Associated With Highly Emetogenic Cancer**
396 **Chemotherapy:** The recommended adult oral dosage of ZOFTRAN is a single 24-mg tablet
397 administered 30 minutes before the start of single-day highly emetogenic chemotherapy, including
398 cisplatin ≥ 50 mg/m². Multiday, single-dose administration of ZOFTRAN 24-mg Tablets has not
399 been studied.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

454 HOW SUPPLIED

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

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

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

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

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

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

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

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

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

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

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

483 REFERENCE

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- 492



493
494 GlaxoSmithKline
495 Research Triangle Park, NC 27709

496
497 ZOFRAN Tablets and Oral Solution:
498 GlaxoSmithKline
499 Research Triangle Park, NC 27709

500
501 ZOFRAN ODT Orally Disintegrating Tablets:
502 Manufactured for GlaxoSmithKline
503 Research Triangle Park, NC 27709
504 by Cardinal Health
505 Blagrove, Swindon, Wiltshire, UK SN5 8RU

506
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508

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-103/S-017

20-605/S-004

20-781/S-001

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number and Name of Drug:

NDA 20-103/S-017; Zofran (ondansetron) Tablets
NDA 20-605/S-004; Zofran (ondansetron) Oral Solution
NDA 20-781/S-001; Zofran ODT (ondansetron) Orally-Disintegrating Tablets

Sponsor: Glaxo Wellcome, Inc.

Material Reviewed

Submission Date(s): October 13, 1999, Final Printed Labeling (FPL)

Receipt Date(s): October 14, 1999

Background and Summary Description: NDA 20-103, approved December 31, 1992, provides for Zofran Tablets. NDA 20-605, approved January 24, 1997, provides for Zofran Oral Solution. NDA 20-781, approved [on draft labeling] January 27, 1999 provides for Zofran ODT Orally-Disintegrating Tablets. All three products share a common package insert and are indicated for the following indications:

1. Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥ 50 mg/m²,
2. Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy,
3. Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen, and
4. Prevention of postoperative nausea and/or vomiting.

(Zofran is also approved in injection and injection premixed formulations; these injectable products share a common package insert.)

NDA 20-103/S-017, 20-605/S-004, and 20-781/S-001 were submitted October 13, 1999 as "Changes Being Effected" and provide for the following revisions to the package insert:

1. A new subsection, entitled "Observed During Clinical Practice," within the ADVERSE REACTIONS section,

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NDA 20-605/S-004

NDA 20-781/S-001

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2. Addition of several new adverse reactions in the Observed During Clinical Practice subsection, and
3. Revisions to the OVERDOSAGE section to provide consistency in wording between the oral and injectable product package inserts.

Note: The FPL submitted with this supplement also includes the revisions necessitated by the approval on draft of NDA 20-781 (provides for the Zofran ODT Orally-Disintegrating Tablet) and the approval on draft of NDA 20-103/S-015 (provides for a new indication: prevention of nausea and vomiting due to highly emetogenic cancer chemotherapy).

Review

The submitted insert (**October 1999, RL-755**) was compared to the currently approved insert (**June 1999; approved on draft with NDA 20-103/S-015, August 27, 1999**). In addition to minor editorial and formatting changes which do not affect the meaning of any information being conveyed, the following revisions have been made:

Note: Throughout this review, added text is indicated by a double underline; deletions are indicated by a strikethrough.

1. Overall: The header has been editorially revised to reflect the availability of a new dosage form, the Zofran ODT Orally-Disintegrating Tablets. (There are numerous other minor editorial revisions throughout the insert which reflect the approval of Zofran ODT as well.)

This is an acceptable revision.

2. DESCRIPTION section:

- a. This section has been modified to include a description of the active ingredient, the chemical structure, and the empirical formula of Zofran ODT.

This revision was requested in the January 27, 1999 approval letter for NDA 20-781, therefore, it is acceptable.

- b. The following paragraph has been added (next to the last paragraph):

“Each 4-mg ZOFRAN ODT Orally Disintegrating Tablet for oral administration contains 4 mg ondansetron base. Each 8-mg ZOFRAN ODT Orally Disintegrating Tablet for oral administration contains 8 mg ondansetron base. Each ZOFRAN ODT Tablet also contains

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the inactive ingredients aspartame, gelatin, mannitol, methylparaben sodium, propylparaben sodium, and strawberry flavor. ZOFRAN ODT Tablets are a freeze-dried, orally administered formulation of ondansetron which rapidly disintegrates on the tongue and does not require water to aid dissolution or swallowing.”

This revision was requested in the January 27, 1999 approval letter for NDA 20-781, therefore, it is acceptable.

3. CLINICAL PHARMACOLOGY section, Pharmacokinetics subsection: The text _____ in this subsection has been revised as follows:

Four and 8-mg doses of either ZOFRAN Oral Solution or ZOFRAN ODT Orally Disintegrating Tablets are bioequivalent to corresponding doses of ZOFRAN Tablets and may be used interchangeably.”

This revision was requested in the January 27, 1999 approval letter for NDA 20-781, therefore, it is acceptable.

4. PRECAUTIONS section:

A new “Information for Patients” subsection has been added. It reads,

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

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

This revision was requested in the January 27, 1999 approval letter for NDA 20-781, therefore, it is acceptable.

5. ADVERSE REACTIONS section:

NDA 20-103/S-017

NDA 20-605/S-004

NDA 20-781/S-001

Page 4

- a. New text has been added to the beginning of this section as follows: “The following have been reported as adverse events in clinical trials of patients treated with ondansetron, the active ingredient of ZOFRAN. A causal relationship to therapy with ZOFRAN has been unclear in many cases.”

On October 20, 1999 Dr. Hugo Gallo-Torres, Medical Team Leader, indicated that this change is acceptable.

- b. The following text has been added immediately after the  table in this section:

“Preliminary observations in a small number of subjects suggest a higher incidence of headache when ZOFRAN ODT Orally Disintegrating Tablets are taken with water, when compared to without water.”

This revision was requested in the January 27, 1999 approval letter for NDA 20-781, therefore, it is acceptable.

- c. A new subsection entitled “Observed During Clinical Practice” has been added. It reads, “**Observed During Clinical Practice:** In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of oral formulations of ZOFRAN. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to ZOFRAN.

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

Hepatobiliary: Liver enzyme abnormalities

Lower Respiratory: Hiccups

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

Skin: Urticaria”

According to Dr. Gallo-Torres on October 20, 1999, these changes are acceptable.

6. OVERDOSAGE section: This section now reads,

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

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NDA 20-605/S-004

NDA 20-781/S-001

Page 5

daily intravenous doses as large as 252 mg have been inadvertently administered without significant adverse events. These doses are more than 10 times the recommended daily dose.

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

According to Dr. Gallo-Torres on October 20, 1999, these changes are acceptable.

7. DOSAGE AND ADMINISTRATION section:

- a. The following text has been added to the beginning of this section:

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

This revision was requested in the January 27, 1999 approval letter for NDA 20-781, therefore, it is acceptable.

- b. In the Prevention of Nausea and Vomiting Associated With Highly Emetogenic Cancer Chemotherapy subsection, Pediatric Use subsection, the applicant has replaced the words "pediatric patients" with the word: /

The applicant should be requested to retain the former wording, in accordance with 21 CFR 201.57 (f)(9). (For consistency, the applicant should be requested to replace / with "pediatric patients" throughout the insert.)

- c. This section has been editorially revised to reflect the availability of the Zofran 4 and 8 mg ODT Orally Disintegrating Tablets.

These changes are acceptable.

8. HOW SUPPLIED section:

NDA 20-103/S-017

NDA 20-605/S-004

NDA 20-781/S-001

Page 6

- a. This section has been modified to reflect the availability of the 4 and 8 mg Zofran ODT Orally-Disintegrating Tablets.

This is an acceptable editorial revision.

- b. For the 24 mg tablet, the phrases have been deleted.

The Division agreed to this revision in a September 7, 1999 teleconference, therefore, it is acceptable.

9. Manufacturer/Distributor Block:

The following has been added to this section:

ZOFRAN Tablets and Oral Solution:
Glaxo Wellcome Inc., Research Triangle Park, NC 27709

ZOFRAN ODT Orally Disintegrating Tablets:
Manufactured for Glaxo Wellcome Inc.
Research Triangle Park, NC 27709
by Scherer DDS
Blagrove, Swindon, Wiltshire, UK SN5 8RU

US Patent Nos. 4,695,578; 4,753,789; and 5,578,628

These are acceptable editorial revisions.

Conclusions

The submitted labeling is acceptable and an approval letter should be drafted. However, at the next printing of the package insert, the applicant should replace all instances of the word with the words "pediatric patients." The Division may be notified of this change in the next annual report.

Regulatory Health Project Manager

NDA 20-103/S-017
NDA 20-605/S-004
NDA 20-781/S-001
Page 7

cc:

Original NDAs
HFD-180/Div. Files
HFD-180/McNeil

draft: mm/April 7, 2000/c:\mydocuments\cso\reviews\20007004-slr.doc
r/d Initials: LTalarico 4/10/00
final: April 11, 2000

CSO REVIEW

GlaxoWellcome

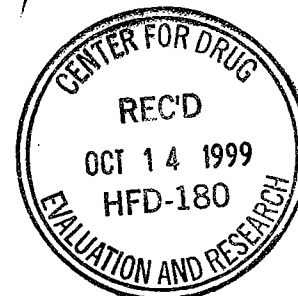
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NDA NO. 20-103 REF. NO. 017
NDA SUPPL FOR HELL

October 13, 1999

Lilia Talarico, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research
Attn: Document Control Room
Office of Drug Evaluation III
Food and Drug Administration
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5600 Fishers Lane
Rockville, MD 20857

*Changes are acceptable
10/20/99
HG-T*



**Re: NDA 20-103; ZOFRAN® (ondansetron hydrochloride) Tablets
NDA 20-781; ZOFRAN® ODT™ (ondansetron) Orally Disintegrating Tablets
NDA 20-605; ZOFRAN® (ondansetron hydrochloride) Oral Solution
Special Supplement: Changes Being Effected, Labeling**

Dear Dr. Talarico:

Reference is made to our New Drug Applications for Zofran Tablets, ODT Tablets, and Oral Solution.

We have completed an extensive review of all spontaneous reports for the oral and injectable Zofran products. The attached revised labeling for the oral products includes a new subsection "Observed During Clinical Practice" under the ADVERSE REACTIONS section. All adverse reactions reported during postmarketing will be included in this section. This section includes several new adverse reactions for which supporting data is being supplied under ATTACHMENTS 2-8. In addition, changes were made to the OVERDOSAGE section to provide consistency in wording between the oral and injectable package inserts. The revised injectable product labeling is being submitted under separate cover.

In accordance with 21 CFR 314.70 (c)(2)(i) and (ii), we are submitting twelve (12) copies of final printed labeling. The package insert will be used at the next printing.

To facilitate your review, a draft package insert is included under ATTACHMENT 1. The package insert is annotated to the supporting data and line-revised to show the new copy underlined and the deleted copy struck through. A diskette of the clean version of the package insert in Word 97 is also attached.

Glaxo Wellcome Inc.

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 483 2100

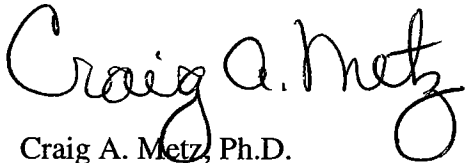
Lilia Talarico, M.D.

October 13, 1999

Page 2

If you have any questions concerning this submission, please contact me at (919) 483-3640.

Sincerely,

A handwritten signature in black ink that reads "Craig A. Metz". The signature is written in a cursive style with a large, looped "C" and "M".

Craig A. Metz, Ph.D.

Director

Regulatory Affairs

NDA 20-103/S-017
NDA 20-781/S-001
NDA 20-605/S-004

Glaxo Wellcome Inc.
Attention: Craig A. Metz, Ph.D.
Director, Regulatory Affairs
Five Moore Drive
Research Triangle Park, NC 27709

Dear Dr. Metz:

We acknowledge receipt of your labeling supplemental applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Supplement Number	Drug Name
20-103	S-017	Zofran (ondansetron) Tablets
20-605	S-004	Zofran (ondansetron) Oral Solution
20-781	S-001	Zofran ODT (ondansetron) Orally-Disintegrating Tablets

Date of Supplements: October 13, 1999

Date of Receipt: October 14, 1999

These supplements propose the following change(s): revision of the package insert to include 1) a new subsection, entitled "Observed During Clinical Practice," within the ADVERSE REACTIONS section, 2) addition of several new adverse reactions in the Observed During Clinical Practice subsection, and 3) revisions to the OVERDOSAGE section to provide consistency in wording between the oral and injectable product package inserts.

Your submission stated that the revised labeling would be implemented at the next printing.

We note that you have submitted these supplements under 21 CFR 314.70(c), 'Special Supplement - Changes Being Effected.'

Unless we notify you within 60 days of our receipt date that the applications are not sufficiently complete to permit a substantive review, these applications will be filed under section 505(b) of the Act on December 13, 1999 in accordance with 21 CFR 314.101(a).

NDA 20-103/S-017

NDA 20-605/S-004

NDA 20-781/S-001

Page 2

Please cite the application numbers listed above at the top of the first page of any communications concerning these applications. All communications concerning these supplemental applications should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Attention: Division Document Room

5600 Fishers Lane

Rockville, Maryland 20857

If you have any questions, contact me at (301) 827-7310.

Sincerely,

Melodi McNeil

Regulatory Health Project Manager

Division of Gastrointestinal and Coagulation Drug

Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research

NDA 20-103/S-017

NDA 20-781/S-001

NDA 20-605/S-004

Page 3

cc:

Archival NDAs 20-103, 20-781, 20-605

HFD-180/Div. Files

HFD-180/M.McNeil

DISTRICT OFFICE

Drafted by: mm/October 25, 1999

final: October 25, 1999

filename: c:\mydocuments\cso\n\20103910-ack.doc

SUPPLEMENT ACKNOWLEDGEMENT (AC)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION**

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS Glaxo Wellcome Inc. Five Moore Drive Research Triangle Park, NC 27709	3. PRODUCT NAME ZOFRAN (ondansetron hydrochloride) Tablets 4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? No IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: ☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. ☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).
2. TELEPHONE NUMBER (Include Area Code) (919) 483-2100	6. LICENSE NUMBER / NDA NUMBER NDA 20-103
5. USER FEE I.D. NUMBER	

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	☒ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE. (See item 7, reverse side before checking box.)
☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, drug, and Cosmetic Act (See item 7, reverse side before checking box.)
☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION	☐ A CRUDE ALLERGENIC EXTRACT PRODUCT
☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY	☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See reverse side if answered YES)

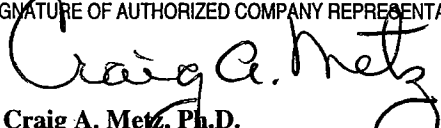
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE  Craig A. Metz, Ph.D.	TITLE Director, Regulatory Affairs	DATE October 13, 1999

FINAL PRINTED LABELING
ZOFRAN® Tablets
(ondansetron hydrochloride)

Package Insert

Labeling: ORIG SEL 017
NDA No: 20-103 Re'd. 10/99
Reviewed by: M. Manuel
4/11/00

6 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ _____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

20-103 897
Withheld Track Number: Administrative- 20-781
5001
20605-5004