CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-781

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-781

GlaxoWellcome Inc.
Attention: Craig Metz, PhD
Director, Regulatory Affairs
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

JAN 27 1999

Dear Dr. Metz:

Please refer to your new drug application (NDA) dated July 1, 1997, received July 2, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zofran ODT (ondansetron) Orally Disintegrating Tablets.

We acknowledge receipt of your submissions dated July 6, 8, 24, and 31, December 4, 1998, and January 7, 1999.

This new drug application provides for the use of Zofran ODT (ondansetron) Orally Disintegrating Tablets for the following indications: prevention of chemotherapy and radiation-induced nausea and vomiting, and prevention of postoperative nausea and vomiting.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted labeling (package insert submitted July 31, 1998, immediate container and carton labels submitted July 31, 1998) with the revisions listed below. Accordingly, the application is approved effective on the date of this letter.

1. Modify the ADVERSE EVENTS section to replace the sentence, "The adverse experience profile seen with Zofran ODT Orally Disintegrating Tablets was similar to that seen with Zofran Tablets." with "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."
2. Revise the following sentence in the PHARMACOKINETICS section to read, "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 interchangeable."

These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-781." Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 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, contact Kati Johnson, Consumer Safety Officer, at (301) 827-7310.

Sincerely,

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-781

FINAL PRINTED LABELING

ZOFRAN®

(ondansetron hydrochloride)

Tablets

ZOFRAN® ODT™

(ondansetron)

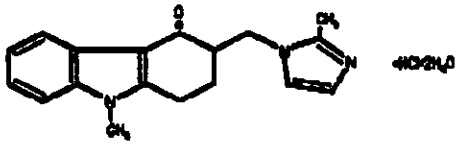
Orally Disintegrating Tablets

ZOFRAN®

(ondansetron hydrochloride)

Oral Solution

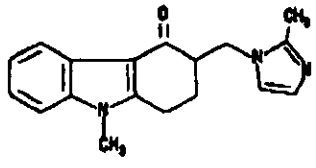
DESCRIPTION: The active ingredient in ZOFRAN Tablets and ZOFRAN Oral Solution is ondansetron hydrochloride (HCl) as the dihydrate, the racemic form of ondansetron and a selective blocking agent of the serotonin 5-HT_3 receptor type. Chemically it is (±) 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, monohydrochloride, dihydrate. It has the following structural formula:



The empirical formula is $C_{18}H_{19}N_3O \cdot HCl \cdot 2H_2O$, representing a molecular weight of 365.9.

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

The active ingredient in ZOFRAN ODT Orally Disintegrating Tablets is ondansetron base, the racemic form of ondansetron, and a selective blocking agent of the serotonin 5-HT_3 receptor type. Chemically it is (±)1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one. It has the following structural formula:



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

Each 4-mg ZOFRAN Tablet for oral administration contains ondansetron HCl dihydrate equivalent to 4 mg of ondansetron. Each 8-mg ZOFRAN Tablet for oral administration contains ondansetron HCl dihydrate equivalent to 8 mg of ondansetron. Each tablet also contains the inactive ingredients lactose, microcrystalline cellulose, pregelatinized starch, hydroxypropyl methylcellulose, magnesium stearate, titanium dioxide, iron oxide yellow (8-mg tablet only), and sodium benzoate (4-mg tablet only).

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 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.

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

CLINICAL PHARMACOLOGY:

Pharmacodynamics: Ondansetron is a selective 5-HT_3 receptor antagonist. While its mechanism of action has not been fully characterized, ondansetron is not a dopamine-receptor antagonist. Serotonin receptors of the 5-HT_3 type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. It is not certain whether ondansetron's antiemetic action is mediated centrally, peripherally, or in both sites. However, cytotoxic chemotherapy appears to be associated with release of serotonin from the enterochromaffin cells of the small intestine. In humans, urinary 5-HIAA (5-hydroxyindoleacetic acid) excretion increases after cisplatin administration in parallel with the onset of emesis. The released serotonin may stimulate the vagal afferents through the 5-HT_3 receptors and initiate the vomiting reflex.

In animals, the emetic response to cisplatin can be prevented by pretreatment with an inhibitor of serotonin synthesis, bilateral abdominal vagotomy and greater splanchnic nerve section, or pretreatment with a serotonin 5-HT_3 receptor antagonist.

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

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

nonconjugated metabolites have pharmacologic activity, these are not found in plasma concentrations likely to significantly contribute to the biological activity of ondansetron.

Oral ondansetron is well absorbed and undergoes limited first-pass metabolism. Following the administration of a single 8-mg ondansetron tablet to healthy, young, male volunteers and from pooled studies, the time to peak plasma ondansetron concentration is approximately 1.7 hours, the terminal elimination half-life is approximately 3 hours, and bioavailability is approximately 56%. Gender differences were shown in the disposition of ondansetron given as a single dose. The extent and rate of ondansetron's absorption is greater in women than men. Slower clearance in women, a smaller apparent volume of distribution (adjusted for weight), and higher absolute bioavailability resulted in higher plasma ondansetron levels. These higher plasma levels may in part be explained by differences in body weight between men and women. It is not known whether these gender-related differences were clinically important. More detailed pharmacokinetic information is contained in the following table taken from one study.

Pharmacokinetics in Normal Volunteers: Single 8-mg ZOFRAN Tablet Dose

Age-group (years)		Mean Weight (kg)	n	Peak Plasma Concentration (ng/mL)	Time of Peak Plasma Concentration (h)	Mean Elimination Half-life (h)	Systemic Plasma Clearance L/h/kg	Absolute Bioavail-ability
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

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

Both AUC and C_{max} more than double on increasing the tablet dose from 8 to 16 mg (123% and 118%, respectively). This may result from saturation of first-pass metabolism leading to greater oral bioavailability at 16 mg than 8 mg.

The administration of oral ondansetron with food increases significantly (about 17%) the extent of absorption of ondansetron. The peak plasma concentration and time to peak plasma concentration are not significantly affected. This change in the extent of absorption is not believed to be of any clinical relevance.

There was no significant effect of antacid administration on the pharmacokinetics of orally administered ondansetron.

Because ondansetron undergoes extensive metabolism, the modest reduction in clearance in the over-75 age-group was not unexpected. However, since there was a difference in neither safety nor efficacy between

patients over 65 years of age and those under 65 years of age, no adjustment in dosage is required in the elderly.

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

CLINICAL TRIALS:

Chemotherapy-Induced Nausea and Vomiting: In one double-blind US study in 67 patients, ZOFRAN Tablets were significantly more effective than placebo in preventing vomiting induced by cyclophosphamide-based chemotherapy containing doxorubicin. Treatment response is based on the total number of emetic episodes over the 3-day study period. The results of this study are summarized below:

Emetic Episodes: Treatment Response

	Ondansetron 8-mg b.i.d. ZOFRAN 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	

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

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

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

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

Emetic Episodes: Treatment Response

	Ondansetron	
	8-mg b.i.d. ZOFRAN Tablets*	8-mg t.i.d. ZOFRAN 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

* The first dose was administered 30 minutes before the start of emetogenic chemotherapy, with a subsequent dose 8 hours after the first dose. An 8-mg ZOFRAN Tablet was administered twice a day for 2 days after completion of chemotherapy.
† The first dose was administered 30 minutes before the start of emetogenic chemotherapy, with subsequent doses 4 and 8 hours after the first dose. An 8-mg ZOFRAN Tablet was administered three times a day for 2 days after completion of chemotherapy.
‡ Median undefined since at least 50% of patients did not have any emetic episodes.
§ Visual analog scale assessment: 0 = no nausea, 100 = nausea as bad as it can be.

Re-treatment: In uncontrolled trials, 148 patients receiving cyclophosphamide-based chemotherapy were re-treated with ZOFRAN Tablets 8 mg t.i.d. of oral ondansetron during subsequent chemotherapy for a total of 396 re-treatment courses. No emetic episodes occurred in 314 (79%) of the re-treatment courses, and only one to two emetic episodes occurred in 43 (11%) of the re-treatment courses.

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

Elderly Patients: One hundred thirty-seven (137) patients 65 years of age or older have received ZOFRAN Tablets. Prevention of emesis was similar to that in patients younger than 65 years of age and adverse reactions were not seen in increased frequency.

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

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

Daily Fractionated Radiotherapy: Ondansetron was significantly more effective than prochlorperazine with respect to complete control of emesis (0 emetic episodes) in a double-blind trial in 135 patients receiving a 1- to 4-week course of fractionated radiotherapy (180 cGy doses) over a field size of ≥100 cm^2 to the abdomen. Patients received the first dose of ZOFRAN Tablets (8 mg) or prochlorperazine (10 mg) 1 to 2 hours before the patient received the first daily radiotherapy fraction, with two subsequent doses on a t.i.d. basis. Patients continued the oral medication on a t.i.d. basis on each day of radiotherapy.

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

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

INDICATIONS AND USAGE:

1. Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.
2. 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.
3. Prevention of postoperative nausea and/or vomiting. As with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and/or vomiting must be avoided postoperatively, ZOFRAN Tablets, ZOFRAN ODT Orally Disintegrating Tablets, and ZOFRAN Oral Solution are recommended even where the incidence of postoperative nausea and/or vomiting is low.

CONTRAINDICATIONS: ZOFRAN Tablets, ZOFRAN ODT Orally Disintegrating Tablets, and ZOFRAN Oral Solution are contraindicated for patients known to have hypersensitivity to the drug.

WARNINGS: Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists.

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

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.

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

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

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

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

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

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

Use in Elderly Patients: Dosage adjustment is not needed in patients over the age of 65 (see CLINICAL PHARMACOLOGY). Prevention of nausea and vomiting in elderly patients was no different than in younger age-groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with ondansetron, the active ingredient of ZOFRAN. A causal relationship to therapy with ZOFRAN has been unclear in many cases.

Chemotherapy-Induced Nausea and Vomiting: The following adverse events have been reported in adults receiving either 8 mg of ZOFRAN Tablets two or three times a day for 3 days or placebo in four trials. These patients were receiving concurrent chemotherapy, primarily cyclophosphamide-based regimens.

Principal Adverse Events in US Trials: 3 Days of Therapy With ZOFRAN Tablets

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%)
Abdominal pain	3 (1%)	13 (3%)	1 (<1%)
Xerostomia	5 (2%)	6 (1%)	1 (<1%)
Weakness	0 (0%)	7 (2%)	1 (<1%)

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

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

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

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

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

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

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

Frequency of Adverse Events From Controlled Studies with ZOFRAN Tablets

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	48 (9%)	35 (7%)
Pyrexia	45 (8%)	34 (6%)
Dizziness	36 (7%)	34 (6%)
Gynecological disorder	38 (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%)

The adverse experience profile seen with ZOFRAN ODT Orally Disintegrating Tablets was similar to that seen with ZOFRAN Tablets.

DRUG ABUSE AND DEPENDENCE: Animal studies have shown that ondansetron is not discriminated as a benzodiazepine nor does it substitute for benzodiazepines in direct addiction studies.

OVERDOSAGE: There is no specific antidote for ondansetron overdose. Patients should be managed with appropriate supportive therapy. Individual intravenous doses as large as 145 mg and total 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.

Hypotension (and faintness) occurred in a patient that took 48 mg of ZOFRAN Tablets. The events resolved completely.

DOSAGE AND ADMINISTRATION:

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.

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

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

Use in the Elderly: The dosage is the same as for the general population.

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

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

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

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

Pediatric Use: There is no experience with the use of ZOFRAN Tablets, ZOFRAN ODT Tablets, or ZOFRAN Oral Solution in the prevention of radiation-induced nausea and vomiting in children.

Use in the Elderly: The dosage recommendation is the same as for the general population.

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

Pediatric Use: There is no experience with the use of ZOFRAN Tablets, ZOFRAN ODT Tablets, or ZOFRAN Oral Solution in the prevention of postoperative nausea and vomiting in children.

Use in the Elderly: The dosage is the same as for the general population.

Dosage Adjustment for Patients With Impaired Renal Function: No specific studies have been conducted in patients with renal insufficiency.

Dosage Adjustment for Patients With Impaired Hepatic Function: In patients with severe hepatic insufficiency, clearance is reduced, apparent volume of distribution is increased with a resultant increase in plasma half-life, and bioavailability approaches 100%. In such patients, a total daily dose of 8 mg should not be exceeded.

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

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

Store between 2° and 30°C (36° and 86°F). Protect from light. Store blisters and bottles in cartons.

ZOFRAN ODT Orally Disintegrating Tablets, 4 mg (as 4 mg ondansetron base) are white, round and plano-convex tablets with no marking on either side in unit dose packs of 30 tablets (NDC 0173-0569-00).

ZOFRAN ODT Orally Disintegrating Tablets, 8 mg (as 8 mg ondansetron base) are white, round and plano-convex tablets with no marking on either side in unit dose packs of 30 tablets (NDC 0173-0570-00).

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

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

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

GlaxoWellcome

Glaxo Wellcome Inc.

Research Triangle Park, NC 27709

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

July 1998 RL-

Submission ~~~~, 7/31/98

Firm informed that this is DRAFT
NDA 20-781

FINAL PRINTED LABELING

ZOFRAN® ODT™
(ondansetron)
Orally Disintegrating Tablets

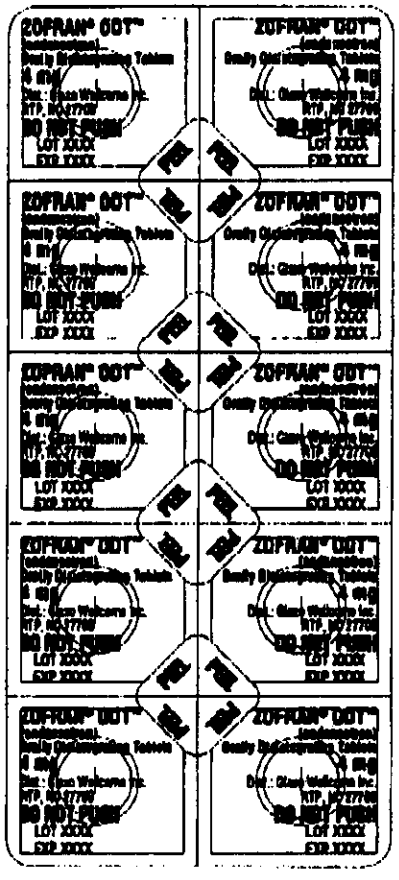
- Foil Blister Backing Material x 4 mg
- Carton x 30 x 4 mg
- Foil Blister Backing Material x 8 mg
- Carton x 30 x 8 mg
- Foil Blister Backing Material x 8 mg Sample
- Blistercard x 1 Sample
- Carton x 5 Blistercards x 1 Sample

NDA 20-781

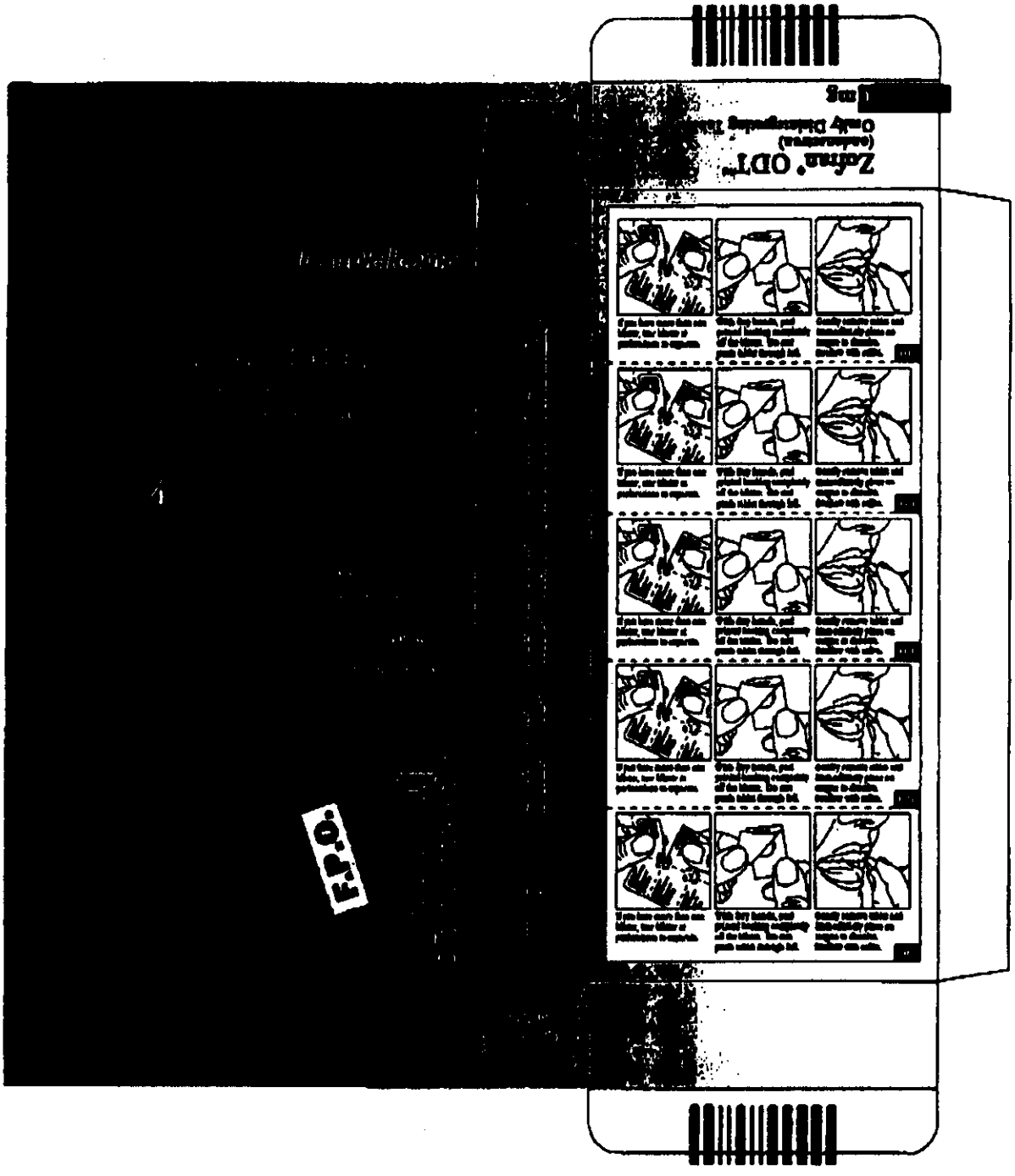
FINAL PRINTED LABELING

ZOFRAN® ODT™
(ondansetron)
Orally Disintegrating Tablets

Foil Blister Backing Material x 4 mg



NDA 20-781
FINAL PRINTED LABELING
ZOFRAN® ODT™
(ondansetron)
Orally Disintegrating Tablets
Carton x 30 x 4 mg

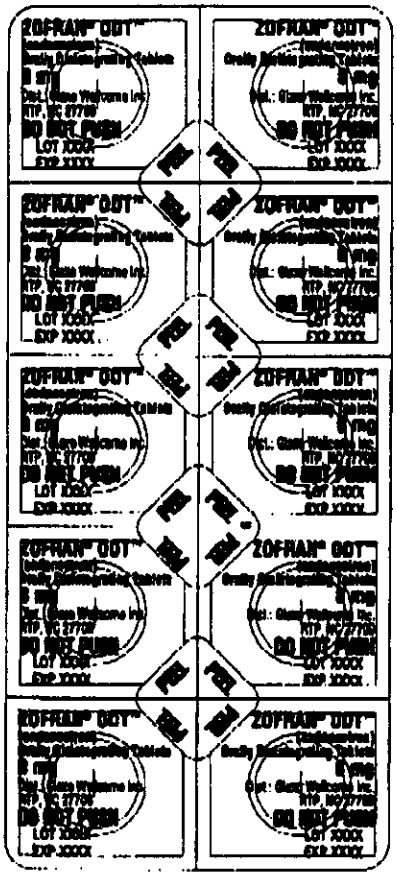


NDA 20-781

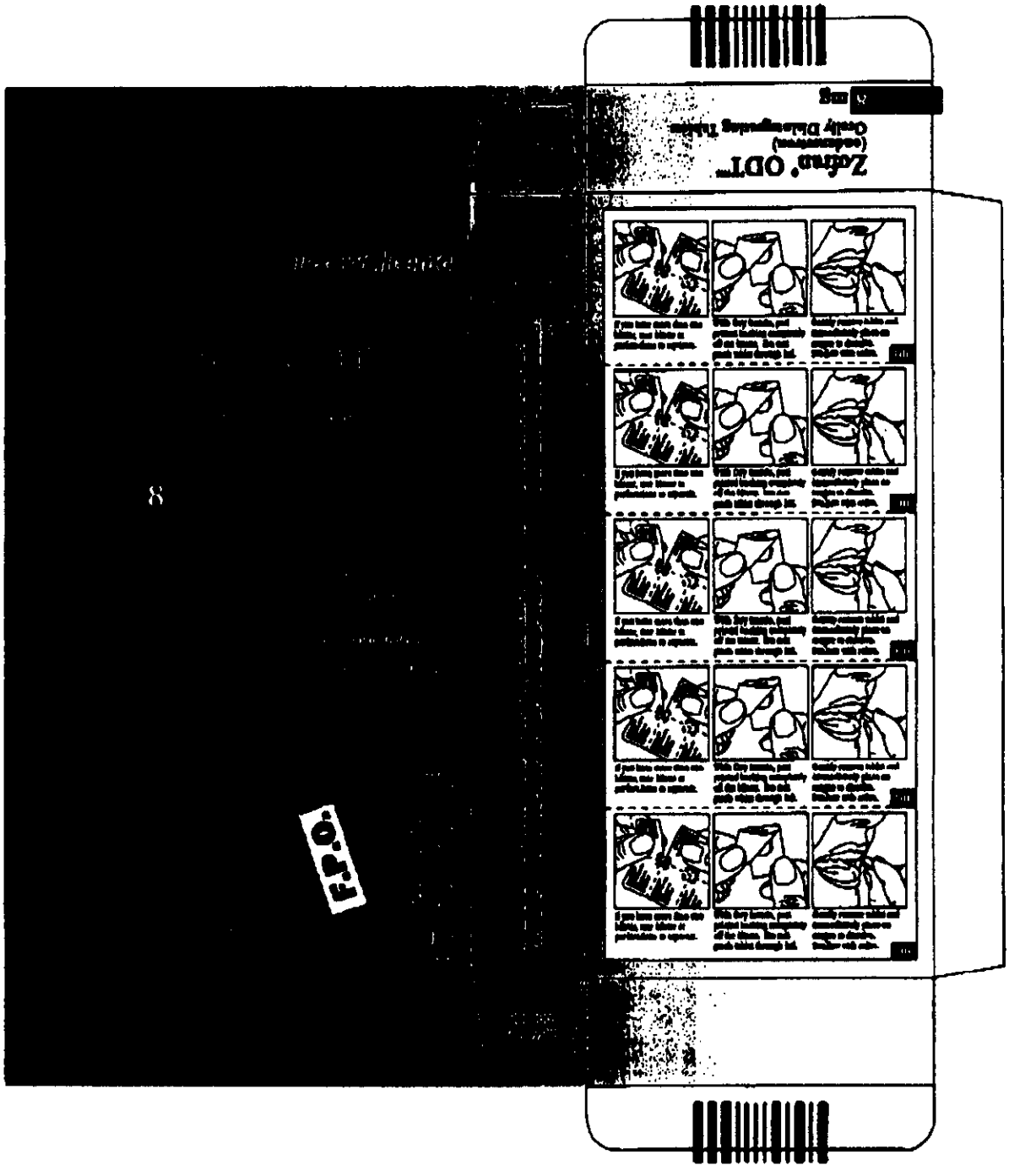
FINAL PRINTED LABELING

ZOFRAN® ODT™
(ondansetron)
Orally Disintegrating Tablets

Foil Blister Backing Material x 8 mg



NDA 20-781
FINAL PRINTED LABELING
ZOFRAN® ODT™
(ondansetron)
Orally Disintegrating Tablets
Carton x 30 x 8 mg

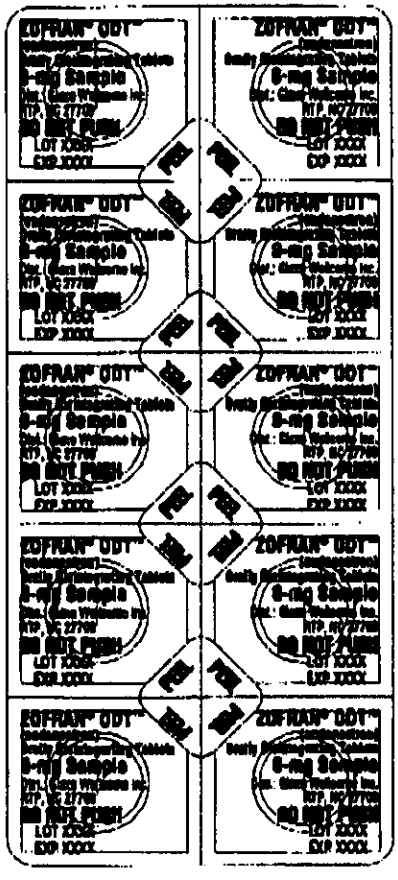


NDA 20-781

FINAL PRINTED LABELING

ZOFRAN® ODT™
(ondansetron)
Orally Disintegrating Tablets

Foil Blister Backing Material x 8 mg Sample



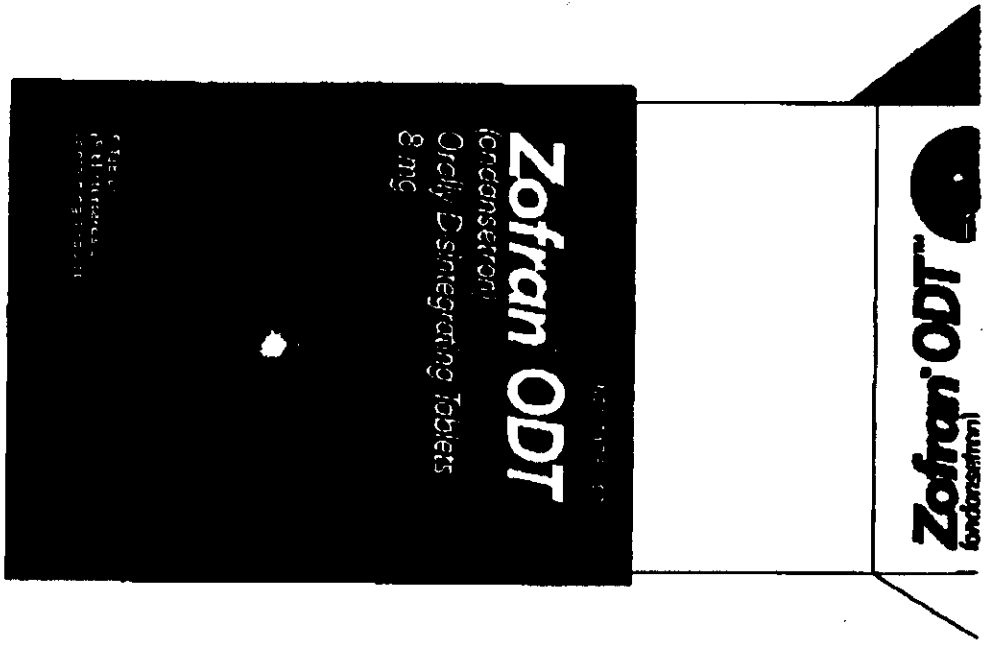
NDA 20-781
FINAL PRINTED LABELING
ZOFRAN® ODT™
(ondansetron)
Orally Disintegrating Tablets
Blistercard x 1 Sample

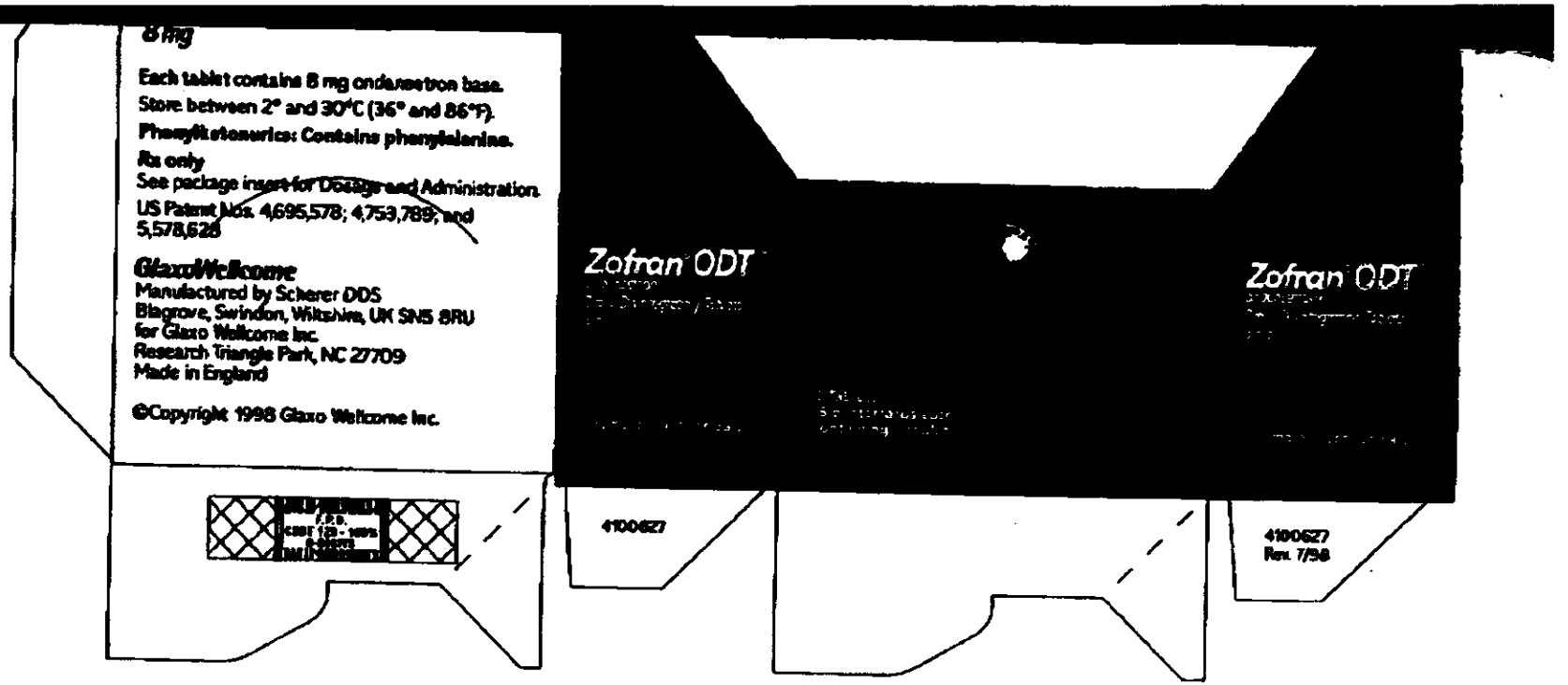
NDA 20-781

FINAL PRINTED LABELING

ZOFRAN® ODT™
(ondansetron)
Orally Disintegrating Tablets

Carton x 5 Blistercards x 1 Sample




8mg
Each tablet contains 8 mg ondansetron base.
Store between 2° and 30°C (36° and 86°F).
Phenylketonurics: Contains phenylalanine.
Rx only
See package insert for Dosage and Administration.
US Patent Nos. 4,695,578; 4,753,789; and 5,578,628
GlaxoWellcome
Manufactured by Scherer DDS
Blagrove, Swindon, Wiltshire, UK SN5 8RU
for Glaxo Wellcome Inc.
Research Triangle Park, NC 27709
Made in England
©Copyright 1998 Glaxo Wellcome Inc.
4100627
Zofran ODT
Zofran ODT
4100627
Rev. 7/98

33 **Page(s) Redacted**

Draft

Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-781

CHEMISTRY REVIEW(S)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA 20-781 **CHEM.REVIEW:** #2 **REVIEW DATE:** 12/23/1998 DEC 23 1998

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	7/1/97	7/7/97	7/9/97
AMENDMENT [AC]	9/26/97	9/29/97	10/6/97
	11/18/97	11/19/97	11/24/97
	4/3/98	4/6/98	-
	6/9/98	6/10/98	6/23/98
	7/24/98	7/27/98	8/6/98

NAME & ADDRESS OF APPLICANT:
Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

DRUG PRODUCT NAME
Proprietary: Zofran Zydis Tablet
Nonproprietary/USAN: Ondansetron
Code Name/#: N/A
Chem.Type/Ther.Class:

ANDA Suitability Petition/DESI/Patent Status:

PHARMACOL.CATEGORY/INDICATION: 5-HT_3 Receptor Antagonist

DOSAGE FORM: Orally Disintegrating Tablet

STRENGTHS: 4 mg, 8 mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: X Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, hydrochloride, dihydrate.

$C_{18}H_{19}N_3O \cdot HCl \cdot 2H_2O$

Mol. wt. = 365.86

For molecular structure see USAN 1995, pg. 485.

SUPPORTING DOCUMENTS:

APPEARS THIS WAY
ON ORIGINAL

NDA 20-103, amendments and supplements - Zofran Tablets
NDA 20-007, amendments and supplements - Zofran Injection

RELATED DOCUMENTS (if applicable):

DMF [redacted]
DMF [redacted]

CONSULTS:

None

REMARKS/COMMENTS:

Three deficiencies that were included in the original review of this NDA, dated June 11, 1998, were satisfied by actions taken by the firm as described in two amendments filed to this NDA by Glaxo Wellcome which were dated April 3, 1998 and June 9, 1998. The rest of the deficiencies, which were communicated to the firm in an Approvable letter dated June 30, 1998, are addressed as part of this amendment.

CONCLUSIONS & RECOMMENDATIONS:

The application may be Approved. There remain two items of concern that should be addressed by the applicant on a post-approval (Phase 4) basis. Those items are described in part H., Draft Comments/Recommendations.

/S/ 12/23/98

Raymond P. Frankewich, Ph.D.
Review Chemist, HFD-180

/S/ 12/23/98

Eric P. Duffy, Ph.D.
Chemistry Team Leader, HFD-180

cc:
Orig. NDA 20-781
HFD-180/Division File
DISTRICT OFFICE
HFD-180/RFrankewich
HFD-180/KJohnson
R/D Init by: EDuffy/
RF/rpf Draft 12-8-98/F/T 12-23-98

APPEARS THIS WAY
ON ORIGINAL

NDA 20-781 CHEMISTRY REVIEW ADDENDUM

DRUG PRODUCT:

SPONSOR: GlaxoWellcome, Inc.

REVIEWER: Ray P. Frankewich, PhD

TEAM LEADER: Eric P. Duffy, PhD

REVIEW:

Chemistry review #2 concluded with a recommendation of approval with a request that the firm make 2 phase 4 commitments. These requests will be instead be made in a correspondence to the firm, and the requested information should be filed in the annual report when available:

CONCLUSION

A correspondence should be sent to the firm with the above comments, and the NDA should be APPROVED.

/S/ 1/27/99

Eric P. Duffy, PhD
Chemistry Team Leader, HFD-180

APPEARS THIS WAY
ON ORIGINAL

APR - 8 1998

TITLE OF DMF:

DMF: **DMF Type:** III

1. CHEM REVIEW # 1 **2. REVIEW DATE:** February 27, 1998

3. DMF INFORMATION REVIEWED

Type of Submission	Date of Submission	Location of Information
Review & Letter (and supporting documents)	December 4, 1997	Vol. 1.1

4. PREVIOUS DOCUMENTS

Type of Document	Date of Document	Description
None		

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

NAME:
ADDRESS:

REPRESENTATIVE:
TELEPHONE:

6. ITEMS REVIEWED:

7. DMF REFERENCED FOR:

NDA:	20-781
APPLICANT NAME:	Glaxo, Inc.
LOA DATE:	October 11, 1996
DRUG PRODUCT NAME:	Zofran® Zydis®
DOSAGE FORM:	Rapidly Disintegrating Tablet
STRENGTH:	4 mg, 8 mg
ROUTE OF ADMINISTRATION:	Oral

8. SUPPORTING DOCUMENTS: DMF and DMF

9. CURRENT STATUS OF DMF:

DATE OF LAST UPDATE OF DMF: December 11, 1995
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED: December 11, 1996

10. CONSULTS: None

11. COMMENTS:

The last review if this DMF was performed on November 12, 1997, by Arthur B. Shaw, Review Chemist, HFD-180, for The items reviewed in that document were the

same ones of interest with this NDA. Five deficiencies were noted in that review. These deficiencies were communicated to the DMF holder in a letter dated December 4, 1997. These deficiencies should be resolved before this DMF can be judged as adequate for the purposes of the approval of NDA 20-781.

12. CONCLUSION:

This DMF is not adequate to support approval of NDA 20-781. Please refer to the review of this DMF of November 12, 1997, by Arthur B. Shaw, Ph.D., Review Chemist, HFD-180, and accompanying letter to the DMF holder dated December 4, 1997.

/S/ 4/8/98
Raymond P. Frankewich, Ph.D.
Review Chemist, HFD-180

/S/ 4/8/98
Eric P. Duffy, Ph.D.
Chemistry Team Leader, HFD-180

cc:
Original DMF (2 copies)
HFD-180/Div. File/NDA 20-781
HFD-180/EDuffy
HFD-180/LTalarico
HFD-181/CSO/KJohnson
R/D init:EDuffy/4-6-98
rpf/dob **F/T 4-6-98**/Wp

APPEARS THIS WAY
ON ORIGINAL

/S/ JUN 11 1998

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA 20-781 **CHEM.REVIEW:** #1 **REVIEW DATE:** March 19, 1998

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	7/1/97	7/7/97	7/9/97
AMENDMENT [AC]	9/26/97	9/29/97	10/6/97
	11/18/97	11/19/97	11/24/97

NAME & ADDRESS OF APPLICANT:
Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

DRUG PRODUCT NAME
Proprietary: Zofran Zydis Tablet
Nonproprietary/USAN: Ondansetron
Code Name/#: N/A
Chem.Type/Ther.Class:

ANDA Suitability Petition/DESI/Patent Status:

PHARMACOL.CATEGORY/INDICATION: 5-HT_3 Receptor Antagonist

DOSAGE FORM: Orally Disintegrating Tablet

STRENGTHS: 4 mg, 8 mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, hydrochloride, dihydrate.

$C_{18}H_{19}N_3O \cdot HCl \cdot 2H_2O$

Mol. wt. = 365.86

For molecular structure see USAN 1995, pg. 485.

SUPPORTING DOCUMENTS:

APPEARS THIS WAY
ON ORIGINAL

NDA 20-103, amendments and supplements - Zofran Tablets
NDA 20-007, amendments and supplements - Zofran Injection

RELATED DOCUMENTS (if applicable):
DMF:
DMF:

CONSULTS:
None

REMARKS/COMMENTS:
See part H., Draft Deficiency Letter.

CONCLUSIONS & RECOMMENDATIONS:
The application is Not Approvable. The major justification for this conclusion is a cGMP violation with one of the facilities invloved in characterizing the drug product (see part H., Draft Deficiency Letter, item 1). Several other deficiencies of a less critical nature are listed in part H.

/S/ 6/11/98
Raymond P. Frankewich, Ph.D.
Review Chemist, HFD-180

/S/ 6/11/98
Eric P. Duffy, Ph.D.
Chemistry Team Leader, HFD-180

cc:
Orig. NDA 20-781
HFD-180/Division File
DISTRICT OFFICE
HFD-180/RFrankewich
HFD-180/KJohnson
R/D Init by: EDuffy/6-9-98
RF/dob Draft 3-19-98/F/T 6-10-98

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ON ORIGINAL

3 **Page(s) Redacted**

Draft

Document

APR - 8 1998

TITLE OF DMF: [redacted]

DMF: [redacted] DMF Type: IV

1. CHEM REVIEW # 1 2. REVIEW DATE: March 18, 1998

3. DMF INFORMATION REVIEWED

Type of Submission	Date of Submission	Location of Information
Amendment	December 13, 1994	Volume 2.1

4. PREVIOUS DOCUMENTS

Type of Document	Date of Document	Description
None		

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

NAME: [redacted]
ADDRESS:

CONTACT PERSON'S NAME:

ADDRESS:
TELEPHONE:

6. ITEM(S) REVIEWED: [redacted]

7. DMF REFERENCED FOR:

NDA:	20-781
APPLICANT NAME:	Glaxo Wellcome, Inc.
LOA DATE:	June 4, 1996
DRUG PRODUCT NAME:	Zofran® Zydis®
DOSAGE FORM:	Rapidly Disintegrating Tablet
STRENGTH:	4 mg, 8 mg
ROUTE OF ADMINISTRATION:	Oral

8. SUPPORTING DOCUMENTS: None

9. CURRENT STATUS OF DMF:

DATE OF LAST UPDATE OF DMF: February 18, 1998
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED: N/A

10. CONSULTS: None

12. **CONCLUSION:**
The DMF is acceptable for the approval of NDA 20-781.

/S/ 4/8/98
Raymond P. Frankewich, Ph.D.
Review Chemist, HFD-180

/S/ 4/8/98
Eric P. Duffy, Ph.D.
Chemistry Team Leader, HFD-180

cc:
Original DMF [redacted] (2 copies)
HFD-180/Div. File/NDA 20-781
HFD-180/EDuffy
HFD-180/LTalarico
HFD-181/CSO/KJohnson
R/D init:EDuffy/4-6-98
rpf/dob **F/T 4-8-98**/Wp

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ON ORIGINAL

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secret and/or

confidential

commercial

information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-781

PHARMACOLOGY REVIEW(S)

020

/S/

NDA 20-781

Reviewer: Gerald A. Young, Ph.D.
Pharmacologist, HFD-180

Review # 1

Sponsor & Address: Glaxo Wellcome Inc.
Research Triangle Park, NC

SEP 12 1996

Date of Submission: July 1, 1997

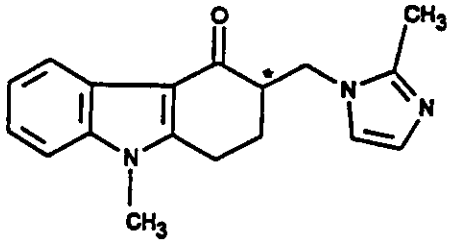
Date of Receipt by HFD-180: July 7, 1997

Date of Review: September 11, 1997

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary

DRUG: ZOFRAN® (ondansetron) ZYDIS® freeze-dried tablets (4 and 8 mg).

(3R,S) 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-1-one.



*Chiral center

$C_{18}H_{19}N_3O$ MW 293.4

CATEGORY: 5-Hydroxytryptamine$_3$ receptor antagonist.

FORMULATION: Ondansetron base and the inactive ingredients gelatin, mannitol, aspartame, methylparaben sodium, propylparaben sodium, strawberry flavor and [redacted]

RELATED NDA: 20-007

PROPOSED MARKETING INDICATION: Prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy; prevention of nausea and vomiting associated with radiotherapy, either total body irradiation, or single high-dose fraction or to the abdomen; and prevention of postoperative nausea and/or vomiting.

DOSE: For the prevention of nausea and vomiting in adults on the day of moderately emetogenic cancer chemotherapy, the recommended oral dosage of Zofran® is 8 mg or 10 ml (2 teaspoonfuls equivalent to 8 mg of ondansetron), given 30 min before the start of emetogenic chemotherapy, with a subsequent dose 8 hours after the first dose. After completion of chemotherapy in adults, the recommended oral dosage of Zofran® is 8 mg or 10 ml or the recommended oral dosage of Zofran® Zydis® is 8 mg given twice a day (every 12 hours) for 1 or 2 days. For patients 12 years of age and older, the dosage is the same as for adults. The dosage for the elderly is the same as for the general population.

For patients 4 through 11 years of age on the day of emetogenic chemotherapy, the recommended oral dosage of Zofran® is 4 mg or 5 ml (1 teaspoonful equivalent to 4 mg of ondansetron) or the recommended oral dosage of Zofran® Zydis® is 4 mg given 30 min before the start of emetogenic chemotherapy, with subsequent doses 4 and 8 hours after the first dose. After completion of emetogenic chemotherapy in patients 4 through 11 years of age, the recommended oral dosage of Zofran® is 4 mg or 5 ml or the recommended oral dosage of Zofran® Zydis® is 4 mg given three times a day (every 8 hours) for 1 or 2 days.

For the prevention of nausea and vomiting associated with radiotherapy in adults, either total body irradiation, or single high-dose fraction or daily fractions to the abdomen; the highest recommended oral dosage for Zofran® is 8 mg or 10 ml and the highest recommended oral dosage of Zofran® Zydis® is 8 mg given three times a day. For total body irradiation, either Zofran® or Zofran® Zydis® should be administered 1 to 2 hours before each fraction of radiotherapy administered each day. For single high-dose fraction radiotherapy to the abdomen, either Zofran® or Zofran® Zydis® should be administered 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy. For daily fractionated radiotherapy to the abdomen, either Zofran® or Zofran® Zydis® should be administered 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for every day radiotherapy is given. There is no experience with the use of Zofran® and Zofran® Zydis® in the prevention of radiation-induced nausea and vomiting in children. The dosage for the elderly is the same as for the general population.

For the prevention of postoperative nausea and vomiting in adults, the recommended oral dosage of Zofran® is two 8-mg tablets or 20 ml of oral solution (4 teaspoonfuls equivalent to 16 mg of ondansetron) or the recommended oral dosage of Zofran® Zydis® is two 8-mg tablets given 1 hour before induction of anesthesia. There is no experience with the use of Zofran® and Zofran® Zydis® in the prevention of postoperative nausea and vomiting in children. The dosage for the elderly is the same as for the general population.

PRECLINICAL STUDIES AND TESTING LABORATORIES:

Type of Study	Study/Report #	Drug Batch #	Testing Laboratory	Page #
Pharmacology	----	---	---	3
Absorption, Distribution, Metabolism & Excretion (ADME): Rats	----	---	---	5
Acute Oral Toxicity in Rats	290121/ NTX/95/012	2 (Base & HCl salt)	[1]TRL	6
1-Month Oral Toxicity in Rats	290221/ NTX/95/017	2/MPD 02266 (Base) Montrose 106 (HCl salt)	[1]TRL	7
Segment II. Oral Teratogenic Study in Rats	100422/ NTX/90/006	C854/52/1 (HCl salt)	[redacted]	10

[1]Tsukuba Research Laboratories, Nippon Glaxo Ltd., JAPAN

PHARMACOLOGY:

The currently approved tablet and oral solution formulations of Zofran® contain the selective 5-Hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonist ondansetron hydrochloride as the dihydrate. Sponsor has developed Zofran® Zydis® Tablets as an oral dosing alternative for the currently approved and marketed formulations of Zofran®. Zofran® Zydis® Tablets contain ondansetron base, rather than ondansetron hydrochloride. Thus, sponsor has submitted comparative preclinical studies on effects of ondansetron base and ondansetron hydrochloride on cisplatin-induced emesis in *Suncus murinus* and the von Bezold-Jarisch reflex in rats. Sponsor has referred to ondansetron as GR38032, the base as GR38032X, and the hydrochloride dihydrate salt as GR38032F.

1. *In Vivo* Studies:

Anti-Emetic Effects of GR38032X and GR38032F on Cisplatin-Induced Emesis in *Suncus murinus*.

The monkey, dog and ferret have been extensively sued as experimental animal models in the testing of drugs for emetic and antiemetic activity. In the late 1980s, the use of the house musk shrew (*Suncus murinus*) was also established as an experimental model for testing of drugs for emetic and antiemetic activity (Life Sci. 1987; **41**: 513-8; Jpn. J. Pharmacol. 1988; **48**: 303-6), and has also been extensively used since the late 1980s.

One advantage of the house musk shrew is its relatively smaller size (approximately 100 g) that allows easier handling and requires smaller quantities of test drugs than the other species.

As shown in the following table for cisplatin-induced emesis in *Suncus murinus*, both GR38032X and GR38032F produced dose-related decreases in no. of animals that vomited/no. of animals tested, mean no. of emetic episodes, and mean duration of emesis, and a dose-related increase in latency to first emetic episode. There were no significant differences between the anti-emetic effects of GR38032X and GR38032F.

Anti-Emetic Effects of GR38032X and GR38032F on Cisplatin-Induced (20 mg/kg, i.p.) Emesis in *Suncus murinus*.

Compound	Dose (mg/kg, p.o.)	No. Vomited/No. Tested	Mean no. of Emetic Episodes	Mean Latency to First Emetic Episode (min)	Mean Duration of Emesis (min)
Vehicle	---	7/7	33.4	44.0	54.9
GR38032X (Ondansetron base)	0.1	7/7	14.9	71.1	19.1
	0.3	6/7	13.6	101.0	21.6
	1.0	0/7	0	180	0
GR38032F (Ondansetron hydro-chloride)	0.1	7/7	15.9	77.4	26.9
	0.3	5/7	8.0	125.6	6.0
	1.0	1/7	1.1	176.1	0.1

Antagonistic Effect of GR38032X and GR38032F on The von Bezold-Jarisch Reflex (transient bradycardia) Induced by 2-methyl-5-HT in Anesthetized Rats.

When rats were anesthetized with urethane (1.25 g/kg, i.p.), artificially respired, and intravenously injected with increasing doses of the 5-HT_3 agonist 2-methyl-5-HT (2.5, 5, 10, 20, 40, 80 and 160 µg/kg) in a volume of 1 ml/kg every 15 min; intraduodenal administration of GR38032X (67, 100, 150 and 225 µg/kg) and GR38032F (67, 100, 150 and 225 µg/kg) inhibited the 2-methyl-5-HT-induced von Bezold-Jarisch reflex (BJR). ID_{50}s were 132.5 and 102.2 µg/kg for GR38032X and GR38032F, respectively. Thus, there was no significant difference between the antagonistic effect of GR38032X and GR38032F on the BJR in anesthetized rats.

ABSORPTION, DISTRIBUTION, METABOLISM & EXCRETION (ADME):

1. Absorption:

Rats

1. Pharmacokinetics of Orally Administered GR38032X and GR38032F.

Animals: Male Sprague-Dawley rats (240-290 g; 7-8 weeks of age).

Methods: Two groups of fifty rats each were orally administered 1 mg base/kg of GR38032X (ondansetron base) and GR38032F (ondansetron hydrochloride), respectively. Vehicle was 0.5% (w/v) aqueous hydroxypropyl methylcellulose solution; dosing volume was 4 ml/kg. Blood samples were obtained via the abdominal aorta from 5 animals per time point at 0.083, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, and 6 hrs after dosing. Plasma concentrations of GR38032X and GR38032F were determined by [redacted]. The pharmacokinetic parameters C_{max}, T_{max} and $T_{½}$ were based upon mean plasma concentration data; $AUC_{0-\infty}$s were calculated by the trapezoidal method.

Results: As shown in the following table, pharmacokinetic parameters for orally administered GR38032X and GR38032F (both at a dose of 1 mg base/kg) were not significantly different.

Pharmacokinetic Parameters for Orally Administered GR38032X (1 mg/kg) and GR38032F (1 mg base/kg) in Male Rats.

Compound	$AUC_{0-\infty}$ (ng base·hr/ml)	C_{max} (ng base/ml)	T_{max} (hr)	$T_{½}$ (hr)
GR38032X	20.79	27.84	0.25	0.58
GR38032F	23.94	39.12	0.25	0.52

TOXICOLOGY:

ACUTE TOXICITY:

Rats

1. Acute Toxicity of Orally Administered GR38032X in Rats (Study No. 290121).

Testing Laboratory: Tsukuba Research Laboratories
Nippon Glaxo Ltd.
JAPAN

Compliance With Good Laboratory Practices and Quality Assurance Requirements: Sponsor provided statement of compliance.

Study Started: September 22, 1994

Study Completed: February 27, 1996

Animals: Male (mean body weight of 138.2 g; 5 weeks of age) and female (mean body weight of 119.6 g; 5 weeks of age) Sprague-Dawley rats

Methods: Rats were orally administered GR38032X (0, 32, 64 and 128 mg/kg); vehicle was 0.5% (w/w) aqueous hydroxypropyl methylcellulose; dosing concentration was 10 ml/kg. There were 10 rats (5 males and 5 females) per group; observation period was 15 days.

Results: Results are summarized in the following table. Orally administered GR38032X produced cyanosis, blepharophimosis, gasping, tremors, and convulsions.

Summary of Acute Toxicity Data for GR38032X in the Rat.

Species	Route of Adm.	Time Until Death	Minimum Lethal Dose (mg/kg)
Rat	Oral	Males: within 1 hr Females: within 3.5 hr	Males: 32 mg/kg Females: 64 mg/kg

The minimal lethal acute oral dose of GR38032F has been shown to be 64 mg/kg in male and female Sprague-Dawley rats (Jpn. Pharmacol. Therap., 20: S995-S998, 1992). Thus, minimal lethal acute oral doses of GR38032X and GR38032F were similar in Sprague-Dawley rats.

SUBACUTE TOXICITY:

Rats

1. 1-Month Oral Toxicity Study of GR38032X and GR38032F (Study No. 290221/Report No. NTX/95/017).

Testing Laboratory: Tsukuba Research Laboratories
Nippon Glaxo Ltd.
JAPAN

Compliance with Good Laboratory Practices and Quality Assurance Requirements: Sponsor provided statements of compliance.

Study Started: January 23, 1995

Study Completed: November 16, 1995

Animals: Male (176.0 to 218.4 g; 6 weeks of age) and female (128.6 to 159.7 g; 6 weeks of age) Sprague-Dawley rats.

Methods: According to the sponsor, selection of the high dosage level of GR38032X was based upon the results of a 28-week oral toxicity study of GR38032F in rats (Study No. R10671; Report No. WPT/86/013) and a reproductive toxicity study of GR38032F in rats (Study No. 100422/Report No. NTX/90/006).

Thus, 4 groups of 24 rats each (12 males and 12 females) were orally administered 0, 1.6, 8 and 40 mg/kg/day of GR38032X, respectively, by gavage for 35 to 36 (males) or 37 to 38 (females) days. Twenty-four rats (12 males and 12 females were orally administered 40 mg base/kg/day of GR38032F for 35 to 36 (males) or 37 to 38 (females) days. In the 40 mg/kg/day dosage groups for GR38032X and GR38032F, animals received 16 mg/kg/day for Days 1-2, 32 mg/kg/day for Days 3-4, and 40 mg/kg/day for Day 5 onwards. Vehicle was 0.5% (w/w) aqueous hydroxypropyl methyl cellulose; dosing concentration ranged from [redacted] mg/ml.

Animals were observed at least twice daily for clinical signs of toxicity and mortality. Body weights were recorded for all animals twice during the pre-treatment period, twice weekly during treatment, and on the day of sacrifice. Food consumption was recorded during the last 4 pre-treatment days, Day 1 of treatment, and twice weekly thereafter during treatment.

Blood samples for hematology and clinical chemistry measurements were obtained by puncture of the abdominal aorta under pentobarbitone anesthesia preceding terminal sacrifice. Animals were not fasted before terminal sacrifice. Urine samples for urinalysis were collected from all animals for 16 hrs in fasted animals once during Days 15 to 18 of treatment and once during Day 29 to 32 of treatment.

Ophthalmic examinations were done for all animals once during the pretreatment period and on one of Days 30 to 33 of treatment.

Animals were sacrificed the day after the final dosing by withdrawal of blood from the abdominal aorta under pentobarbitone anesthesia. All animals were subjected to gross pathological examination. Organ weights were recorded for lungs, adrenals, brain, liver, ovaries, spleen, testes, thymus, prostate, heart, kidneys and pituitary.

Tissue samples from heart, aorta, trachea, lungs, tongue, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, pancreas, salivary glands, femur, sternum, spleen, thymus, lymph nodes, kidneys, urinary bladder, pituitary, parathyroids, thyroids, adrenals, testes, epididymides, prostate, seminal vesicles, ovaries, uterus, vagina, cerebrum, cerebellum, spinal cord, sciatic nerve, eyes, Harderian glands, skin, mammary glands, skeletal muscle and diaphragm were subjected to histopathological examination in all control and high dose animals at terminal sacrifice.

When appropriate, data were subjected to one-way analyses of variance, Bartlett's test, and Kruskal-Wallis test.

Results:

1. Observed Effects: There were treatment-related increases in % incidence of partially closed eyes (3.0%) in the males of the 40 mg/kg/day GR38032X dosage group, and treatment-related increases in % incidence of salivation (1.4%), subdued behavior (0.4%) and prone position (0.2%) in males of the 40 mg/kg/day GR38032F dosage (Comparative) group. There were treatment-related increases in % incidence of salivation (0.2%), subdued behavior (0.9%), tremor (0.4%) and partially closed eyes (0.2%) in females of the 40 mg/kg/day GR38032X dosage group, and treatment-related increases in % incidence of salivation (1.5%), subdued behavior (1.0%), tremor (0.3%) and prone position (0.4%) in females of the 40 mg/kg/day GR38032F dosage (Comparative) group.

2. Mortality: There were 3 deaths (2 males and 1 female) in the 40 mg/kg/day GR38032X dosage group on Days 14, 15 and 23, respectively. None of these 3 animals displayed any clinical signs of toxicity before death. On the other hand, gross pathological and histopathologic examinations of these 3 animals did not implicate dosing error as the cause of death.

There were 4 deaths (2 males and 2 females) in the 40 mg/kg/day GR38032F dosage group on Days 29, 30, 7 and 25, respectively. One male displayed prone position, gasping, piloerection, sedation and convulsions before death. Moreover, gross pathological and histopathologic examinations of the other 3 animals implicated dosing error as the cause of death.

Thus, GR38032X administration may have contributed to the deaths of 3 animals at the 40 mg/kg/day dose, and GR38032F administration may have contributed to the death of 1 animal at the 40 mg/kg/day dose.

3. Body Weight: Mean body weights of control males and females were 195.7 and 150.2 g, respectively, on Day 1 of treatment. Mean body weights of control males and females were 416.0 and 248.2 g, respectively, on Day 36 of treatment. There were no treatment-related effects on body weight.

4. Food Consumption: Mean food consumption of control males and females was 26 and 19 g/animal/day, respectively, on Day 1 of treatment. Mean food consumption of control males and females was 30 and 18 g/animal/day, respectively, on Day 32 of treatment. There were no treatment-related effects on food consumption.

5. Hematology: There were no treatment-related effects.

6. Blood Chemistry: Alanine aminotransferase levels were increased in males receiving 40 mg/kg/day of GR38032X (30.1%; % of difference from control) and GR38032F (24.7%). Alanine aminotransferase levels were increased in females receiving 40 mg/kg/day of GR38032X (18.7%) and GR38032F (16.5%). There were no other treatment-related effects.

7. Urinalysis: There were no treatment-related effects.

8. Ophthalmology: There were no treatment-related effects.

9. Organ Weights: There were no treatment-related effects.

10. Gross Pathology: There were no treatment-related incidences of gross pathological lesions.

11. Histopathology: There were no treatment-related incidences of histopathological lesions in males. There were questionable incidences of thymic hemorrhages in both control and high-dose (GR38032X and GR38032F) females. There were no other treatment-related incidences of histopathological lesions in females.

In summary, the no effect oral dose of GR38032X in rats was 8 mg/kg/day. The 40 mg/kg/day doses of GR38032X and GR38032F produced clinical signs of toxicity, mortality, and increases in blood levels of alanine aminotransferase. No target organs of toxicity were identified. Thus, there were no differences in the toxicity produced by GR38032X and GR38032F in a 1-month oral toxicity study in rats.

REPRODUCTIVE TOXICOLOGY:

In a Segment II. oral teratogenic study (Report No. NTX90/006; Study No. 100422) of GR38032F (0, 2.5, 10 and 40 mg/kg/day from Day 7 through Day 17 of gestation) in pregnant Sprague-Dawley rats, GR38032F was not teratogenic. Furthermore, there were no treatment-related effects on the reproductive performance of the F_1 generation, and there was no teratogenicity in female pregnant rats of the F_1 generation.

For comparison, in a Segment II. oral teratogenic study of ondansetron maleate (0, 1, 4 and 15 mg/kg/day from Day 7 through Day 16 of gestation) in pregnant AHA rats, ondansetron maleate was not teratogenic (Pharmacologist's Review of NDA 20-007 dated May 18, 1990).

Thus, orally administered GR38032F (ondansetron hydrochloride dihydrate) and ondansetron maleate were not teratogenic in the pregnant rat. It should be noted, however, that employed doses, durations of drug treatment, and rat species differed between these two Segment II. teratogenic studies.

PROPOSED TEXT OF THE LABELING FOR ZOFRAN® ZYDIS® TABLETS:

A. The sponsor has proposed the following text for the **Carcinogenesis, Mutagenesis, Impairment of Fertility:** section of the labeling:

"Carcinogenesis, Mutagenesis, Impairment of Fertility:

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

The reviewer recommends the following modified text for the **Carcinogenesis, Mutagenesis, Impairment of Fertility:** section of the labeling:

"Carcinogenesis, Mutagenesis, Impairment of Fertility:

B. The sponsor has proposed the following text for the **Pregnancy: Teratogenic Effects: Pregnancy Category B:** section of the labeling:

"Pregnancy: Teratogenic Effects: Pregnancy Category B:

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

The reviewer recommends the following modified text for the **Pregnancy: Teratogenic Effects: Pregnancy Category B:** section of the labeling:

"Pregnancy: Teratogenic Effects: Pregnancy Category B:

C. The sponsor has proposed the following text for the **DRUG ABUSE AND DEPENDENCE:** section of the labeling:

"DRUG ABUSE AND DEPENDENCE:

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

The reviewer does not recommend any changes.

The sponsor has proposed the following text for the **OVERDOSAGE:** section of the labeling:

"OVERDOSAGE: There is no specific antidote for ondansetron overdose. Patients should be managed with appropriate supportive therapy. Individual intravenous doses as large as 145 mg and total daily intravenous doses as large as 252 mg have been inadvertently administered without adverse events. These doses are more than 10 times the recommended daily dose.

Hypotension (and faintness) occurred in a patient that took 48 mg of ZOFRAN Tablets. The events resolved completely."

The reviewer does not recommend any changes.

SUMMARY AND EVALUATION:

Zofran® (ondansetron hydrochloride, GR38032F) is a selective 5-HT_3 receptor antagonist that is currently approved for the prevention of nausea/vomiting associated with emetogenic cancer chemotherapy and radiotherapy, and for the prevention of postoperative nausea and/or vomiting. Zofran® is available in a tablet formulation, intravenous injection formulation, and an oral solution formulation. Sponsor has developed Zofran® Zydis® Tablets as an oral dosing alternative for the currently approved and marketed formulations of Zofran®. Zofran® Zydis® Tablets contain ondansetron base (GR38032X) in a palatable, freeze-dried tablet that disperses rapidly on the tongue and does not require water to aid dissolution or swallowing.

Sponsor previously submitted preclinical pharmacology and toxicity data for ondansetron in support of NDA 20,007 that was previously reviewed and evaluated (Pharmacologist's Review dated May 18, 1990). The original NDA submission included preclinical pharmacology studies, ADME studies in mice, rats, dogs and rabbits; acute i.v. and oral toxicity studies of ondansetron hydrochloride dihydrate in mice and rats; 2-week (ondansetron maleate) and 5-week (ondansetron hydrochloride dihydrate) i.v.

toxicity studies in rats and dogs; 5-week and 7-week (ondansetron maleate), and 28-week and 18-month (ondansetron hydrochloride dihydrate) oral toxicity studies in rats; 5-week (ondansetron maleate), and 28-week and 12-month (ondansetron hydrochloride dihydrate) oral toxicity studies in dogs; a 103-week oral carcinogenicity study of ondansetron hydrochloride dihydrate in $C57/B_1$ mice; and a 104-week oral carcinogenicity study of ondansetron hydrochloride dihydrate in Sprague-Dawley rats. Mutagenicity studies of ondansetron hydrochloride dihydrate included the Ames test in *Salmonella typhimurium*, gene conversion assay in *Saccharomyces cerevisiae*, WHO nitrosation assay in *Salmonella typhimurium*, forward mutation assay in Chinese hamster ovary cells, cytogenic assay in human lymphocytes, and the micronucleus test in mice. Reproductive toxicity studies included a Segment I. oral fertility and reproductive performance study of ondansetron hydrochloride dihydrate in rats, Segment II. i.v. (ondansetron hydrochloride dihydrate) and oral (ondansetron maleate) teratogenic studies in rats and rabbits, and a Segment III. peri- and postnatal study of ondansetron hydrochloride dihydrate in rats. Special toxicity studies of ondansetron hydrochloride dihydrate included a 7-day i.v. irritancy study in rats, intramuscular and subcutaneous local irritancy study in rabbits, contact allergenicity study in guinea pigs, and an *in vitro* hemolysis and plasma compatibility test.

Since the present submission for Zofran® Zydis® Tablets is based on the pharmacokinetics and bioavailability of Zofran® Zydis® Tablets compared to conventional Zofran® Tablets, sponsor submitted comparative preclinical studies using ondansetron base (GR38032X) versus ondansetron hydrochloride (GR38032F). Thus, the present NDA submission included comparative pharmacological, ADME, and acute and 1-month oral toxicity studies in rats. A Segment II. teratogenic study of ondansetron hydrochloride dihydrate (GR38032F) in rats was also included in the NDA submission.

Preclinical pharmacological studies demonstrated that GR38032X and GR38032F had similar dose-response (0.1 to 1.0 mg/kg, p.o.) anti-emetic effects on cisplatin-induced emesis in *Suncus murinus* (house musk shrew) and had similar antagonistic effects (ID_{50}s of 132.5 and 102.2 µg/kg, respectively), when administered intraduodenally, on the von Bezold-Jarisch reflex induced by 2-methyl-5-HT in anesthetized rats. Thus, there were no differences between the pharmacological effects of GR38032X and GR38032F in rats in these studies.

In a single-dose pharmacokinetic comparison of orally administered GR38032X and GR38032F in rats, $AUC_{0-\infty}$s were 20.79 and 23.94 ng base•hr/ml, C_{max}s were 27.84 and 39.12 ng base/ml, T_{max}s were 0.25 and 0.25 hr, and $T_{½}$s were 0.58 and 0.52 hr, respectively. Thus, there were no differences between the pharmacokinetics of orally administered GR38032X and GR38032F in rats.

In acute oral toxicity studies in rats, minimal lethal doses for GR38032X were 32 and 64 mg/kg in males and females, respectively, and minimal lethal doses for GR38032F were 64 mg/kg/day in both males and females. Orally administered GR38032X and GR38032F produced tremors and convulsions that were associated with other clinical signs of toxicity (cyanosis, gasping and bradypnea) that suggested a state of anoxia. Thus, there were no differences between the acute toxic effects of orally administered GR38032X and GR38032F in rats.

In a 1-month oral toxicity study of GR38032X (0, 1.6, 8 and 40 mg/kg/day) and GR38032F (40 mg/kg/day) in rats, the no effect oral dose of GR38032X was 8 mg/kg/day. The 40 mg/kg/day doses of GR38032X and GR38032F produced clinical signs of toxicity, mortality, and increases in blood levels of alanine aminotransferase. No target organs of toxicity were identified. Thus, there were no differences in the toxicity produced by GR38032X and GR38032F in a 1-month oral toxicity study in rats.

In the Segment II. teratogenic study of orally administered GR38032F (0, 2.5, 10 and 40 mg/kg/day) in pregnant female rats, GR38032F was not teratogenic in the F_0 generation. Furthermore, there were no treatment-related effects on the reproductive performance of the F_1 generation, and there was no teratogenicity in female pregnant rats of the F_1 generation. These results are comparable to those for a Segment II. oral teratogenic study in female rats that was included in the original submission for NDA 20,007.

In summary, the above comparative preclinical studies of GR38032X and GR38032F (pharmacology, pharmacokinetic, acute and 1-month oral toxicity) support the NDA application for Zofran® Zydis® Tablets that is based on the pharmacokinetics and bioavailability of Zofran® Zydis® Tablets compared to conventional Zofran® Tablets.

Finally, the reviewer has suggested a modified text for the **"Carcinogenesis, Mutagenesis, Impairment of Fertility:"** and **"Pregnancy: Teratogenic Effects: Pregnancy Category B:"** sections of the labeling

RECOMMENDATIONS:

From a preclinical viewpoint, the NDA is approvable.

/S/ 9/11/97

Gerald A. Young, Ph.D.
Pharmacologist, HFD-180

/S/

9/12/97

cc:
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary
HFD-180/Dr. Talarico
HFD-180/Dr. Young
HFD-345/Dr. Viswanathan

R/D Init.: J. Choudary 9/4/97

GAY/hw/9/11/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-781

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Memorandum

Office of Clinical Pharmacology and Biopharmaceutics

NDA: **20-781**

Title: Zofran-Zydis® Tablet *Rx*. (Ondansetron)

Reviewer: Alfredo R. Sancho, Ph.D. Ref.: Phase IV Sponsor Commitments
Submission Date: 01 Jul. 1997

Dosage: Oral 4mg/8mg Tablet. Prevention of nausea and vomiting associated with Chemotherapy-induced emesis (CIE), Radiotherapy-induced emesis (RIE) and Postoperative nausea and/or vomiting (PONV).

Sponsor: Glaxo Welcome Inc.
Address: Five Moore Drive, Research Triangle Park, NC 27709

BACKGROUND

Prior to the completion of the NDA review a memorandum detailing a reviewer's request to the sponsor was issued on June 12, 1998. The review of NDA 20-781 itself was completed on June 29, 1998. A final supplement document for this NDA detailing the reviewer's comments on the sponsor's response to our review recommendations (June 29, 1998) was completed on January 15, 1999. According to the Project Manager (PM) for this NDA all final comments to the sponsor need to be sent to the sponsor no later than January 27, 1999.

There was a direct telephone conversation between this reviewer and the representative for the sponsor, Ms. Linda Haberer, on May 12, 1998 (1300 hrs EST). Documentation of this conversation and the requests of the reviewer for the sponsor are detailed in memorandum dated June 12, 1998.

Two conversations occurred between this reviewer and the team leader Medical Officer of this clinical division, HFD-180. These meetings occurred on December 14, 1998 and January 25, 1999. The two same issues were discussed in both meetings. These were the need and wording of a short paragraph related to the safety of this drug product when it is taken with water or water is given to the patient immediately after dosing ("wash-down") and the need and benefits of an additional dissolution test that would mimic the oral cavity in humans.

Based on all the written documentation related to this NDA submission, the contact with the sponsor, the response of the sponsor, the meetings with the clinical division team leader medical officer, and the meetings with other OCPB staff members, the following are the conclusions and recommendations of this reviewer.

CONCLUSIONS

1. The issue of the dissolution method used for this drug product is still not resolved. The sponsor has not responded in an adequate manner to our comments and insists that their dissolution method is appropriate for this drug product. The method described and used by the

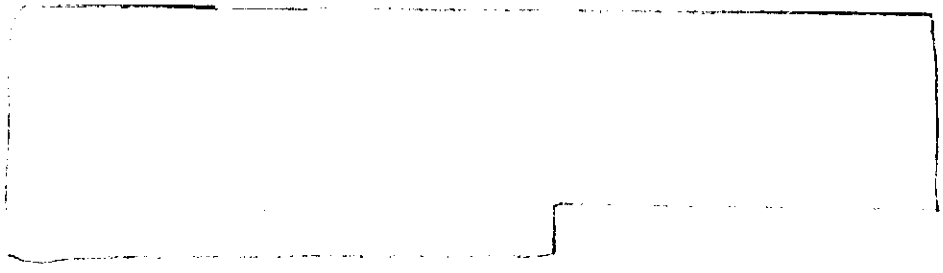
sponsor uses a media with low pH (1% HCl). This low pH is not commonly found in the oral cavity of patients. The drug product presented in this NDA submission is described as a "rapid disintegrating" formulation that occurs in the mouth. The absorption "presumably" occurs, according to the sponsor, in the gastric area and not in the mouth (buccal absorption). The sponsor has not presented any evidence that there is no buccal absorption. Because this drug product first dissolves in the mouth and is later absorbed in the stomach, TWO distinct dissolution methods are requested.

2. Using recommended dosing instructions, the differences in the mean-time-to-peak-concentration (T_{max}) for Zydis 4 mg versus Zofran 4 mg and Zydis 8 mg versus Zofran 8 mg are 15 minutes and 3 minutes, respectively. This may be the reason for a higher incidence of adverse events in all subjects receiving Zydis with water. The number of subjects included in these clinical trials was limited. The original text of this safety related paragraph was too "strong" based on the limited and initial data, hence why Dr. Gallo Torres and I rewrote the text as a compromise with the sponsor. This new text states that the information available is initial and limited in nature. Moreover, just because the sponsor said that all references to taking this drug product with water are deleted from the package insert and label it does NOT take away the possibility that these adverse side events MAY still occur in patients taking this drug product with water or water to "wash-down" the residual taste.

RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics Division of Pharmacologic Evaluation II has reviewed the information and data submitted with this NDA on July 1, 1997. Based upon an evaluation of the provided information and data it is concluded that:

1. Due to safety concerns, observed adverse events, and the limited data to prove or disprove any correlation between these adverse events with the administration of water to patients at the time of dosing or immediately after, the following statement should be included in the Adverse Events/Safety section, so to make physicians and patients aware of possible side effects. If further data is available to clarify this concern, it should be submitted to the Agency.



2. Regarding the in-vitro dissolution information and data that has been provided in this NDA submission, it is felt that additional testing is required. This additional dissolution test should mimic the conditions and environment commonly found in the oral cavity of humans. This could be obtained as a post-approval commitment with the sponsor. It is further recommended that the sponsor contact the Agency to discuss the specifics of what is needed (*e.g.* appropriate media).

/S/ 1/26/99

Alfredo R. Sancho, Ph.D.
Pharmacologist/Pharmacokinetic Reviewer
Radiopharmaceuticals and Imaging Section
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics
Concurrence:

/S/ 1/26/99

David Lee, Ph.D
Team Leader, Pharmacokineticist
Gastrointestinal and Blood Clotting Section
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Cc: HFD-180 NDA 20-781 (1x); DIV.FILE (1x); JOHNSON (1X); SANCHO (1X); LEED (1X); GALLOTORRES (1X)
HFD-870 JHUNT (1x); MLCHEN (1x)
HFD-850 SHUANG
CDR Attn.: Barbara Murphy

APPEARS THIS WAY
ON ORIGINAL

Memorandum

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-781 JUN 12 1998

Title: Zofran-Zydis® Tablet *Rx*. (Ondansetron)

Reviewer: Alfredo R. Sancho, Ph.D. Serial No.: 000
Submission Date: 01 July 1997 Review Date: 01 July 1998
Dosage: Oral 4mg/8mg Tablet. Prevention of nausea and vomiting associated with Chemotherapy-induced emesis (CIE), Radiotherapy-induced emesis (RIE) and Postoperative nausea and/or vomiting (PONV).

Sponsor: Glaxo Welcome Inc.
Address: Five Moore Drive
Research Triangle Park, NC 27709

Synopsis

As a follow up from the May 12th 1998 (1:00 pm EST) telephone conversation with Ms. Linda Haberer (Sponsor's contact person) we would appreciate if the sponsor responded the following comments.

Comments to the Sponsor

1. For a thorough bioequivalence assessment in study Protocol No. 517/410 the sponsor should provide the following AUC, C_{max}, t_{max}, $t_{1/2}$ comparison between:
   - Treatment "*Zofran with water*" and Treatment "*Zydis without water*",
   - Treatment "*Zydis without water*" and "*Zydis with water*", and
   - Treatment "*Zofran with water*" and "*Zydis with water*".

   These comparisons (mean ratios, 90%CI, and p-values) should be done using the Agency's current criteria (*i.e.* "Two-Sided Tests procedure" or "90% Confidence Intervals") as described in the publication "*A Comparison of the Two One-Sided Tests Procedure and the Power Approach for Assessing the Equivalence of Average Bioavailability*" by Donald J. Schuirmann in the Journal of Pharmacokinetics and Biopharmaceutics, Volume 15, No. 6, 1987. The sponsor should also provide the statistical outputs for the comparisons of C_{max} and AUC ANOVA, where the model used for this ANOVA include, at least, the sources of variability from subject, sequence, subjects nested in sequence, period, and treatment.

2. For a proper bioequivalence assessment in submitted studies, the AUC to the last-detectable drug plasma concentration (AUC_{0-t}) is often used. Therefore the sponsor should submit for study Protocol No. 517/410, the pk parameter AUC_{0-t} as a function of the last-detectable drug plasma concentration, as well as the Two Sided Test procedure to asses bioequivalence between all three treatments in this study.

3. It is not clearly stated in the submission if the drug lots used for all treatments and in all three studies are: (*1*)the to-be-marketed formulation; (*2*)from commercial size batches, or from a batch at least [ ] that of a commercial size, or from a batch that contains at least [ ] tablets; and

(3)are the site/s of manufacturing of the drug lots used in these studies the same sites where the commercial batches are to be manufactured.

4. How and where in the proposed label will the observed greater intersubject variability (maximum-minimum ranges, medians, and means for t_{max}, AUC, and C_{max}) in subjects receiving Zydis tablets with water as compared to Zofran tablets with water; and the slightly higher PK parameters values in this off-label use (8 mg Zydis tablet with 150 ml of water treatment) be presented. Particularly the issue that there is a higher incidence of adverse events (50% higher) reported among healthy subjects and that this incidence of adverse events is expected to be the same if not higher in the indented population for this drug.

5. The calculated pharmacokinetic parameters and the statistical analysis for the study Protocol No. 032X-01, need to be recalculated and submitted following the guidelines for bioequivalency studies, or as described in the following reference "A Comparison of the Two One-Sided Tests Procedure and the Power Approach for Assessing the Equivalence of Average Bioavailability" by Donald J. Schuirmann in the Journal of Pharmacokinetics and Biopharmaceutics, Volume 15, No. 6. 1987. Provided also should be the statistical outputs for the comparisons of C_{max} and AUC ANOVA, where the model used for this ANOVA include, at least, the sources of variability from subject, sequence, subject nested in sequence, period, and treatment.

The sponsor should send their response to the above comments and other pertinent information directly to Kati Johnson, the assigned CSO for this submission.

/S/

Alfredo R. Sancho, Ph.D.
Pharmacologist/Pharmacokinetic Reviewer
Gastrointestinal and Coagulation Drug Section
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

/S/

John Hunt
Team Leader, Pharmacokineticist
Gastrointestinal and Coagulation Drug Section
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Cc: HFD-180 NDA 20-781 (1x); DIV.FILE (1x); KJOHNSON (1X); ASANCHO (1X); JHUNT (1X)
HFD-870 JHUNT (1x); MLCHEN (1x)
HFD-850 SHUANG
CDR Attn.: Barbara Murphy

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-781 - Supplement

Title: Zofran-Zydis® Tablet *Rx*. (Ondansetron) JAN 15 1999

Reviewer: Alfredo R. Sancho, Ph.D. Re.: *Response to Approvable Letter*

Submission Date: 31 July, 1998 Type of Submission: Label Supplement

Dosage: Oral 4mg/8mg Tablet. Prevention of nausea and vomiting associated with Chemotherapy-induced emesis (CIE), Radiotherapy-induced emesis (RIE) and Postoperative nausea and/or vomiting (PONV).

Sponsor: Glaxo Welcome Inc.

Address: Five Moore Drive, P. O. Box 13398
Research Triangle Park, NC 27709

In the Agency's Approvable Letter (July 1, 1998) sent to the sponsor, the following two comments were included (bold print) as part of the Clinical Pharmacology, Pharmacokinetics section.

- **Revise the Pharmacokinetics subsection of the CLINICAL PHARMACOLOGY section. Modify the statement;**

-

The sponsor subsequently responded to the Agency's Approvable Letter (July 31, 1998). The arguments presented by the sponsor in response to the first bold print statement included in the original Agency's Approvable Letter, do not address directly these observed mentioned changes in the PK parameters between ZOFRAN ODT (previously ZOFRAN RDT) when given with and without water. The sponsor argues in length the bioequivalency between the two different formulations, which is not an issue. The sponsor intends to address the observed slight increase in Cmax (at least 5%) and slight decrease in Tmax (at least 6 minutes) when this drug product (same dose size and formulation) is given with water as compared to when it is given without water with the following statement:

> *"In order to provide for consistency with the intended administration of this Ondansetron formulation, the package insert has been revised to delete references to*

In relation to the above second bold print statement, the sponsor argues in length that the observed slight increase in adverse event of headaches and dizziness are not related to this drug product, as determined by the investigator. This determination is first of a subjective nature, and second these observed adverse events need to be viewed in relation to the slight changes of this drug product PK parameters when given with water and without water (slight increase in Cmax, and slight decrease in Tmax).

The following are some of the concluding facts stated in the original NDA 20-781 review:

- The new 4 mg and 8 mg Zydis tablets when given **with** and/or **without** 150 ml of water, are bioequivalent to the 4 mg and 8 mg Zofran tablets, respectively. The new Zydis formulation and its two dosage sizes fall within the 90% CI for the 2 one sided test for Cmax of Ondansetron plasma levels. In addition, the new Zydis formulation and its two dosage sizes fall within the 90% CI for the 2 one sided test for AUC of Ondansetron plasma levels.
- The "*time of the sample in which the maximum measured plasma Ondansetron concentration occurred*" or t_{max} results from all three studies and across all treatments, suggest that there is a quicker and higher exposure to Ondansetron from Zydis tablets when given with water, as compared to Zydis without water or to Zofran tablets with water. This may be the reason for a higher incidence of adverse events in all subjects receiving Zydis with water.

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics Division of Pharmacological Evaluation II has reviewed the information and data submitted with this NDA on July 1, 1997. This office has further reviewed the sponsor's response to the Agency's Approval Letter and has concluded that:

1. As stated before, the new freeze dry 4 mg and 8 mg tablet formulations of Ondansetron base, Zofran Zydis, are equivalent in extent of absorption (*i.e.* C_{max} and AUC_{∞}) to the reference formulation or respective marketed Zofran 4 mg and 8 mg tablets. Using recommended dosing instructions, the differences in the mean-time-to-peak-concentration (T_{max}) for Zydis 4 mg versus Zofran 4 mg and Zydis 8 mg versus Zofran 8 mg are 15 minutes and 3 minutes, respectively. The number of subjects included in these clinical trials was limited, and [redacted] if any statement regarding taking this drug product with water is included in the package insert or any where else in the labeling, a safety statement needs to be incorporated in the Adverse Events/Safety section, so to make physicians and patients aware of possible side effects:

2. The sponsor did not respond to the Agency's concerns regarding the in-vitro dissolution information and data that has been provided in this NDA submission. This could be obtained post-approval and it is recommended that the sponsor contact the Agency to discuss the specifics of what is needed (*e.g.* appropriate media).

/S/ for Alfredo Sancho 1/15/99

Alfredo R. Sancho, Ph.D.
Pharmacologist/Pharmacokinetic Reviewer
Radiopharmaceuticals and Imaging Section
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

/S/ 1/15/99 ★ Note

David Lee, Ph.D.
Team Leader, Pharmacokineticist
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Cc: HFD-160 NDA 20-781 (1x); DIV.FILE (1x); JOHNSON (1X); SANCHO (1X); LEE (1X)
HFD-870 JHUNT (1x); MLCHEN (1x)
HFD-850 SHUANG
CDR Attn.: Barbara Murphy

Enclosures: [Click here and type number]

Attachments: [Click here and type number]

★ Note: Since the Applicant stated that "the package insert has been revised to delete [redacted] Dr. Alfredo Sancho's Comment #1 may not be forwarded to the Applicant at this time, unless the Medical Division feels that it is necessary to do so. However, as per Comment #2, the ~~Sponsor~~ Applicant needs to respond to the Agency's request on dissolution information.

/S/ 1/15/99.

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-781 JUN 29 1998

Title: Zofran-Zydis® Tablet *Rx.* (Ondansetron)

Reviewer: Alfredo R. Sancho, Ph.D. Serial No.: 000

Submission Date: 01 Jul. 1997 Type of Submission: New Dosage Form (1P)

Dosage: Oral 4mg/8mg Tablet. Prevention of nausea and vomiting associated with Chemotherapy-induced emesis (CIE), Radiotherapy-induced emesis (RIE) and Postoperative nausea and/or vomiting (PONV).

Sponsor: Glaxo Welcome Inc.

Address: Five Moore Drive
Research Triangle Park, NC 27709

Synopsis

Zofran Zydis Tablets were developed as an oral dosing alternative for the currently approved and marketed formulations of Zofran. Zofran Zydis Tablets are a freeze-dried, oral administration formulation of Ondansetron which is proposed to disperse rapidly on the tongue of patients without the need of water to aid in dissolution or swallowing. The proposed indication for this tablet is for the prevention of nausea and vomiting associated with Chemotherapy-induced emesis (CIE), Radiotherapy-induced emesis (RIE) and Postoperative nausea and/or vomiting (PONV). The sponsor states in this submission that Zydis, "*Due to its low solubility in saliva, Ondansetron base, in lieu of Ondansetron hydrochloride dihydrate, as found in the currently marketed forms of Zofran, will be employed in the formulation for Zofran Zydis Tablets.*" This change in formulation is supposed to only make the new tablet more palatable without changing the efficacy and biodistribution.

Technical Background

Zofran Zydis Tablets (Ondansetron base) manufacturing is identical to that currently approved for Zofran Injection and Zofran Tablets (Ondansetron hydrochloride dihydrate), up through production of intermediate grade Ondansetron. Zofran Zydis Tablets are then formed by freeze-drying (process which removes the [redacted] excipient portion) an [redacted] of Ondansetron base (instead of the hydrochloride dihydrate salt) in combination with various inactive excipients (*ie.* gelatin, mannitol, aspartame, methylparaben sodium, propylparaben sodium, strawberry flavoring, [redacted]. These excipients are stated by the sponsor to be "*commonly used*", *e.g.* [redacted] Strawberry Flavor Master File Number [redacted] from the [redacted] Zofran Zydis formulation is expected to rapidly disperse on the tongue of patients without the need of water to aid in dissolution or swallowing.

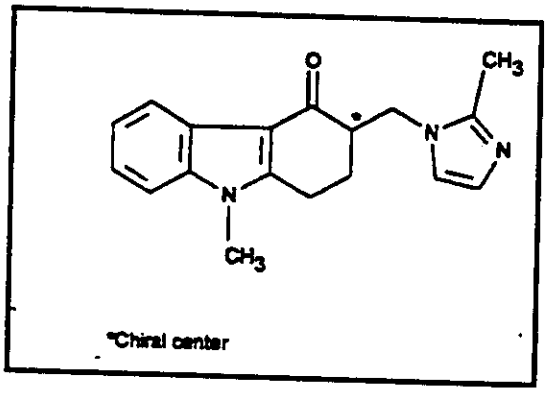
Zofran tablets each contain the inactive ingredients lactose, microcrystalline cellulose, pregelatinized starch, hydroxypropyl methylcellulose, magnesium stearate, titanium dioxide, iron oxide yellow (in 8 mg tablets only), and sodium benzoate (in 4 mg tablets only).

Composition comparison of 4 mg and 8 mg Zydis tablets.

Ingredient	Unit Amounts (mg/unit) 4 mg	8 mg
Active ingredient Ondansetron	4.00	8.00
Inactive ingredients Gelatin		
Mannitol		
Aspartame		
Methylparaben Sodium		
Propylparaben Sodium		
Strawberry Flavour		

APPEARS THIS WAY ON ORIGINAL

Chemically, Zofran (Ondansetron hydrochloride), is (±) 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, monohydrochloride, dihydrate. The empirical formula is $C_{18}H_{19}N_3O \cdot HCl \cdot 2H_2O$, representing a molecular weight of 365.9. Ondansetron HCL dihydrate is a white to off-white powder that is soluble in water and normal saline. Chemically, Zydis (Ondansetron base), is (3R,S) 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one. The empirical formula is $C_{18}H_{19}N_3O$, representing a molecular weight of 293.4. It has the following structure:



Ondansetron, as the hydrochloride dihydrate (Zofran), is currently approved in the following four preparations:

- NDA 20-007, Zofran Injection - 2 mg/ml;
- NDA 20-403, Zofran Injection premixed - 32 mg/50 ml in 5% Dextrose;
- NDA 20-103, Zofran Tablets - 4 mg & 8 mg; and,
- NDA 20-605, Zofran Oral solution - 4 mg/ml.

Pharmacodynamics

Ondansetron is a selective 5-HT_3 receptor antagonist, and its mechanism of action has not been fully characterized. It is not a dopamine-receptor antagonist. Serotonin receptors of the 5-HT3 type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. It is not clear whether Ondansetron's antiemetic action is

mediated centrally, peripherally, or in both sites. However, cytotoxic chemotherapy appears to be associated with the release of serotonin from the enterochromaffin cells of the small intestine. For instance in human patients receiving cisplatin therapy, urinary 5-HIAA (5-hydroxyindoleactic acid) excretion increases in parallel with the onset of emesis, leading to the conclusion that released serotonin may stimulate the vagal afferents through the 5-HT_3 receptors and initiate vomiting reflex.

Ondansetron hydrochloride dihydrate (Zofran) Pharmacokinetics

Ondansetron is extensively metabolized in humans throughout their body. Approximately 5% of a radiolabled dose is recovered from the urine as the parent compound. Although the primary metabolic pathway is hydroxylation on the indole ring followed by subsequent glucuronide or sulfate conjugation, some non-conjugated metabolites have pharmacological activity, but the latter species are not found in plasma concentrations likely to significantly contribute to the biological activity of Ondansetron. Oral Ondansetron is well absorbed and undergoes limited first-pass metabolism in the liver.

Following a **single dose** of **8 mg Ondansetron tablet** to **healthy young male** volunteers the time-to-peak plasma Ondansetron concentration is approximately 1.7 hours, the terminal elimination half-life is approximately 3 hours, and the bioavailability (after first-pass hepatic metabolism) is approximately 56%. Gender differences were shown in the disposition of Ondansetron given as a single dose. The extent and rate of Ondansetron's absorption is greater in women than men. Slower clearance in women, a smaller apparent volume of distribution (adjusted weight), and higher absolute bioavailability resulted in higher plasma Ondansetron levels. Nonetheless, these gender-related differences are not viewed as clinically important.

Table 1. Pharmacokinetics in Normal Volunteers: Single 8 mg ZOFRAN Tablet Dose

Age-group (years)	Mean Weight (kg)	n	C_{max} (ng/ml)	t_{max} (hr)	$t_{1/2}$ (hr)	Systemic Plasma Clearance (l/hr/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	0.770	0.619
F	67.6	6	46.1	2.1	6.2	0.249	0.747

Ondansetron as the hydrochloride dihydrate, is currently approved in the following presentations: Zofran Injection (2 mg/ml), Zofran Injection Premixed (32 mg/50ml in 5% Dextrose), Zofran Tablets (4 mg and 8 mg), and Zofran Oral Solution (4 mg/ml). Both AUC and C_{max} more than double on increasing the tablet dose from 8 to 16 mg (123% and 118% respectively). This may result from saturation of first-pass metabolism leading to greater oral bioavailability at 16 mg than 8 mg. The administration of oral Ondansetron with food increases significantly (≈ 17%) the extent of absorption of Ondansetron. The peak plasma concentration and time to peak plasma concentration are not significantly affected. This change in the extent of absorption is not believed to be of any clinical relevance. There was no significant effect of antacid administration on the pharmacokinetics of orally administered Ondansetron. Furthermore, because Ondansetron undergoes extensive metabolism, there was a modest reduction in clearance in the over-75 age-group. The plasma protein binding of Ondansetron, as measured in-vitro was 70 - 76 percent, this over a concentration range from [redacted] ng/ml.

In a double-blind, 3-day study using 8 mg Zofran tablets, Zofran was shown to be significantly more effective than placebo in preventing (0 emetic episodes) vomiting induced by cyclophosphamide-based chemotherapy containing doxorubicin (61% vs. 6% prevention respectively, $p<0.001$). In another double-blind study using 8 mg Zofran tablets either *b.i.d.* or *t.i.d.*, showed that there was no statistically significant increase in effectiveness (0 emetic episodes) with the increased dosage frequency (61% vs. 58% prevention respectively). Prevention of emetic episodes in the special populations of pediatrics and geriatrics was similar to that in patients between the ages of 18 and 65, with no increase in adverse event reports.

Labeling

The labeling section of the submission uses the approved label for Zofran tablets and Zofran Oral solution with certain modification and additions for the specifics of Zydis tablets. Under the label section "Drug Interactions", the sponsor states that "*Because Ondansetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes, inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of Ondansetron.*"

Objectives

- To demonstrate that the use of Ondansetron base (Zydis) rather than the hydrochloride dihydrate salt (Zofran) does not affect the dissolution and rate of absorption of Ondansetron from the new Zydis formulation tablet.
- To examine the bioequivalence of 4 mg and 8 mg Zydis (Ondansetron base) tablets against 4 mg and 8 mg Zofran (Ondansetron hydrochloride dihydrate salt) tablets.
- To asses bioavailability of Ondansetron Zydis formulation taken without water relative to conventional Zofran tablet taken with water.
- To evaluate the effect of co-administered water on the bioavailability of Ondansetron from the Zydis formulation given without water.

Submitted Study Designs

Dosage

The studies included in this submission used randomized, open-label cross-over designs with two or three treatments depending on the study. The treatments were Oral-lingual administration of either 4 mg or 8 mg Zydis (Ondansetron base) tablets (with and/or without 150 ml of water co-administration) and 4 mg or 8 mg Zofran (Ondansetron) tablets with 150 ml of water, respectively. Between treatment administrations there were of washout periods of 3 to 7 days. Each subject was randomly placed in different treatment groups. During the first bioequivalence study the subjects were told to remain semi-recumbent for 2 hours post dosing. Subjects were also instructed to not consume alcohol nor use tobacco products during the studies.

Protocol

A total of three studies were submitted in this NDA; a pilot study (Protocol C94-010, Report GCP/94/010), a pivotal bioequivalence study (Protocol 517/410, Report UCP/95/053), and a second pivotal bioequivalence study (Protocol 032X-01, Report JJB/96/001). Subjects were fasted prior to each treatment. They were allowed no food nor liquids 8 to 24 hours prior to treatment. Subjects were allowed 200 ml of water upon rising the day of treatment. No food nor liquids were allowed until 4 to 5 hours post treatment dosing. The pilot study had 6 healthy male human subjects between the ages of 18 to 40. The first bioequivalence study had 24 healthy human subjects, 12 female and 12 male, between the ages of 18 to 40. The second bioequivalence study had 30 healthy male subjects between the ages of 20 to 30. Inclusion criteria included written consent, hepatitis B and HIV negative test results, healthy (according a physical exam and laboratory test), negative for HBs antigen and HC antibody, and of any ethnic background. Exclusion criteria included history of allergies, drug, tabacco and alcohol abuse, participation in another study within the previous 30 days, or have donated 450 ml of blood within the previous 3 months. Withdraw criteria included clinically significant adverse effects of the study drug, intercurrent illness, or voluntary withdrawal.

Safety

Prior to each treatment in each of the three studies, each subject had the following procedures done: a 12-lead ECG, blood pressure, pulse rate, oral temperature, respiratory rate, and laboratory test (including hematology, biochemistry, and urinalysis). When applicable, female subjects also had a serum beta HCG pregnancy test performed.

PK/PD Sampling Time Points

Urine samples were obtained from subjects pre and post dosing for urinalysis. Blood samples from each subject were taken for the pre/post-dosing laboratory tests (hematology and biochemistry) and during the studies (at discrete time points) to assay for Ondansetron plasma concentrations. Venipuncture using a red top Vacutainer with no anticoagulant was used to collect 7 to 10 ml of whole blood. Samples were allowed to clot by standing at room temperature for 30 to 60 minutes, after which they were centrifuged at 1500 G for 15 minutes to separate the plasma from other blood components. Samples were kept at -18°C and assayed for Ondansetron levels. Whole blood samples were collected as described in the following tables (minutes and hours separately):

Table 2. Time point distribution for the first 120 minutes in each of the studies.

Study	20	30	40	60	80	90	100	120
C/94/010	x		x	x	x		x	x
517/410	x		x	x		x		x
032X-01		x		x		x		x

Table 3. Time point distribution after the first 120 minutes in each of the studies.

Study	2.5	3	3.5	4	5	6	7	8	9	10	12	16	24
C/94/010	x	x	x	x	x	x	x	x	x	x			
517/410	x	x		x		x	x	x		x	x	x	x
032X-01		x		x		x		x		x	x		x

PK Analytical Methods

All PK parameters were derived from each subject from the plasma Ondansetron concentrations. The calculated PK parameters were the maximum measured plasma Ondansetron concentration (C_{max}); the time of the sample in which C_{max} was measured (t_{max}); the terminal plasma half-life ($t_{1/2}$); and, the area of the curve of plasma Ondansetron concentration versus time, extrapolated to infinite time ($AUC_{0-\infty}$). The Ondansetron levels were assayed using

The analytical methods and their limits of quantification or sensibility used to assay biological samples for Ondansetron from all three studies included in this NDA submission are summarized in the following table:

Table 4. Analytical methods for Ondansetron levels in blood samples.

Study	Biological Fluid	Assay Method	Method Sensitivity (Validated Assay Range)	Specificity
C94-010				
517/410				
032 X-01				

Results

Demographics

Within the subjects included in all three studies, there were several individuals that were reported to be smokers, former smokers, tobacco users, and consumers of alcohol in different degrees. They were instructed to abstain from using alcohol and tobacco substances during the study. The demographic data distribution and dietary pre/post treatment procedures are summarized as follows (means and ranges when appropriate).

Table 5. Demographic analysis of subjects.from all three studies

Study	Washout time	Fasting Pre-dose	Fasting Post-dose	Gender	Age	Weight
C/94/010	72 hours	24 hours	4 hours	6 male	31.2 28 - 34	79.0 67.7 - 88.6
517/410	3 - 7 days	8 hours	5 hours	12 male 13 female	27 18 - 38	66.8 52.4 - 83.7
032X-01	7 days	21 hours	4.5 hours	30 male	24.5 20 - 30	64.4 52.5 - 95.0

Drug lots

A comparison of the three studies and each of their tier groups with dose, dosage form, strength and lot number for test drug used is summarized in the next table.

Table 6. Manufacturing summary on both drugs used in all three studies.

Study	Group	Dose	Dosage Form	Strength	Lot No.
C/94/010	Zofran w/150 ml of water	8 mg	Zofran	8 mg Ondansetron	B0293MD
	Zydis w/150 ml of water	8 mg	Zydis	8 mg Ondansetron	096-4AFD077*
	Zydis w/o water	8 mg	Zydis	8 mg Ondansetron	096-4AFD077*
517/410	Zofran w/150 ml of water	8 mg	Zofran	8 mg Ondansetron	B0293MD
	Zydis w/o water	8 mg	Zydis	8 mg Ondansetron	94J020C
	Zydis w/150 ml of water	8 mg	Zydis	8 mg Ondansetron	94J020C
032X-01	GG032 w/150 ml water	4 mg	Zofran	4 mg Ondansetron	4C152A
	GG032X w/o water	4 mg	Zydis	4 mg Ondansetron	94J030B

**No information was provided on whether the Zydis tablet was the to-be-marketed formulation.*

It is not clear if the Zydis product lot (096-4AFD0077) used in the pilot study No. C/94/010 was the to-be-marketed formulation. The Zydis (8 mg Ondansetron) drug product lots used in the pivotal bioequivalence study I, No. 517/410, was the proposed commercial formulation. The proposed 8 mg tablet commercial batch size will be of [redacted] The Zydis product lot No. 94J020C used in the pivotal bioequivalence study I came from a nominal batch size of [redacted] representing [redacted] of the proposed commercial size batch. The 4 mg Zydis tablet used in the second bioequivalence study, No. 032X-01, was also of the proposed commercial formulation. The Zydis tablets used in this study were from a nominal size batch of [redacted] Both of the batches were manufactured at the same site [redacted] and on the same equipment that will be used to manufacture the Zydis commercial product.

Pharmacokinetic Parameters

A summary of the calculated PK parameters (means with SD, and ranges) for all treatments from all three studies presented in this NDA submission is given in the following table. This summary is presented by study and each of the treatments within each study.

Table 7. Summary of calculated PK parameters for all three studies.

Study	Group	No.	$AUC_{0-\infty}$ (ng.hr/ml)	C_{max} (ng/ml)	t_{max} (hr)	$t_{1/2}$ (hr)
C/94/010	8 mg Zofran w/150 ml of water	6	125 ±33.26	24.3 ±7.86	1.3 ±0.63	3.37 ±0.75
	8 mg Zydis w/150 ml of water	6	160.1 ±47.39	29.4 ±9.37	1.2 ±0.41	3.94 ±1.06
	8 mg Zydis w/o water	6	152.0 ±78.35	23.8 ±6.56	1.6 ±0.41	3.65 ±1.47
517/410	8 mg Zofran w/150 ml of water	24	204 ±33.2	32.0 ±10.1	2.13 ±0.63	4.36 ±0.89
	8 mg Zydis w/o water	24	204 ±33.6	31.8 ±9.4	2.08 ±0.52	3.89 ±0.93
	8 mg Zydis w/150 ml of water	24	206 ±34.2	33.7 ±13.3	2.02 ±0.77	3.80 ±0.97
032X-01	4 mg Zofran w/150 ml water	30	88.64 ±55.56	12.59 ±5.83	2.16 ±0.71	4.31 ±2.17
	4 mg Zydis w/o water	30	89.61 ±37.34	13.30 ±5.74	2.41 ±0.82	4.49 ±1.86

Bioequivalency

For the bioequivalency analysis the 90% confidence intervals using the two one-sided test procedure for all three treatments was followed. The results are presented in the following table.

Table 8. Summary table for the Bioequivalence study I (Study No. 517/410).

		Treatment A		Treatment B		Treatment C	
		8 mg Zofran tablet w/150ml of water	B/A	8 mg Zydis tablet w/o water	C/B	8 mg Zydis tablet w/150ml of water	C/A
AUC_{∞}	*Mean*	204		204		206	
ng.hr/ml	*Range*	[redacted]		[redacted]		[redacted]	
	±SD	33.2		33.6		34.2	
	CV	71		72		74	
	Mean Ratio		1.03		1.02		1.01
	90% CI		0.99-1.08		0.97-1.07		0.97-1.06
C_{max}	*Mean*	32.0		31.8		33.7	
ng/ml	*Range*	[redacted]		[redacted]		[redacted]	
	±SD	10.1		9.4		13.3	
	CV	30.1		28.5		33.2	
	Mean Ratio		1.03		1.07		0.96
	90% CI		0.98-1.09		1.02-1.14		0.91-1.01
t_{max}	*Mean*	2.13		2.08		2.02	
hr	*Range*	[redacted]		[redacted]		[redacted]	
	±SD	0.63		0.52		0.77	
	CV	29.7		25.2		38.2	
	95% CI	1.0-4.0		1.8-2.3		1.8-2.3	
$t_{1/2}$	*Mean*	4.36		3.89		3.80	
hr	*Range*	[redacted]		[redacted]		[redacted]	
	±SD	0.89		0.93		0.97	
	CV	20.1		23.3		24.8	
	Mean Ratio		0.92		0.87		1.05
	90% CI		0.87-0.97		0.82-0.93		0.99-1.11

Table 9. Summary table for the Bioequivalence study II (Study No. 032X-01).

		Treatment A		Treatment B
		4 mg Zofran tablet w/150ml of water	B/A	4 mg Zydis tablet w/o water
AUC_∞	*Mean*	88.64		89.91
ng.hr/ml	*Range*	[redacted]		[redacted]
	±SD	55.56		37.34
	CV			
	Mean Ratio		1.014	
C_{max}	*Mean*	12.59		13.30
ng/ml	*Range*	[redacted]		[redacted]
	±SD	5.83		5.74
	CV			
	Mean Ratio		1.056	
t_{max}	*Mean*	2.16		2.41
hr	*Range*	[redacted]		[redacted]
	±SD	0.71		0.82
$t_{1/2}$	*Mean*	4.31		4.49
hr	*Range*	[redacted]		[redacted]
	±SD	2.17		1.86
	CV			
	Mean Ratio		1.042	

Dissolution & Dispersion Time

Upon review of the dissolution and dispersion methods and data submitted with this NDA, it is unclear the details of the methods used. It is also unclear if the methods used to asses dispersion and dissolution of the new formulation are the most adequate or applicable based on the proposed site of administration, oral-sublingual route.

Chemistry

The composition characteristics of the two proposed dosage strengths of Zydis tablets, 4 mg and 8 mg, were compared. Based on the data submitted, it was found that the Zydis 4 mg and 8 mg tablets are compositionally proportional.

Safety

All three studies had no serious adverse events reported nor deaths. In the pilot study no subjects were withdrawn during the study, only one subject had a "panic-attack" during the treatment regimen with Zofran tablet given with water. During the first bioequivalence study, Zydis with water treatment, one subject withdrew due to severe "stomach pain." Also during the first bioequivalence study, there were 5 reports of adverse events (*e.g.* headaches and dizziness) in treatment A (Zofran with water); 6 reports of adverse events (*e.g.* headaches, dizziness, and stomach ache) in treatment B (Zydis without water); and, 12 reports of adverse events (*e.g.* headache, dizziness, nausea, and stomach ache) in treatment C (Zydis with water).

Table 10. Summary of adverse events documented for all three studies and separated by treatment.

Study	Group	Dose	Adverse event/s	Withdrawn	Withdraw cause
C/94/010	Zofran w/150 ml of water	8 mg	0	1	"panic-attack"
	Zydis w/150 ml of water	8 mg	0	0	
	Zydis w/o water	8 mg	0	0	
517/410	Zofran w/150 ml of water	8 mg	5	0	
	Zydis w/o water	8 mg	6	0	
	Zydis w/150 ml of water	8 mg	12	1	"stomach pain"
032X-01	Zofran w/150 ml of water	4 mg	2	0	
	Zydis w/o water	4 mg	2	0	

Conclusions

- Ondansetron is intended to prevent nausea and vomiting associated with Chemotherapy-induced emesis (CIE), Radiotherapy-induced emesis (RIE), and Postoperative nausea and/or vomiting (PONV). Ondansetron, when given in either the Zofran tablet with water or the Zydis tablet without water and under fasting conditions or without special diets, seems to be well tolerated among healthy (male and female) subjects.
- The percent extrapolation from AUC_{0-t} to $AUC_{0-\infty}$ were all within 10% in the pivotal study protocol 517/010.
- The sponsor provided adequate information on the assay system used to measure Ondansetron levels in blood samples and the quality control procedures followed to asses sensitivity and reproducibility of such measurements.
- The new 8 mg Zydis tablets when given **with** and/or **without** 150 ml of water, is bioequivalent to the 8 mg Zofran tablets. The new 4 mg Zydis tablets when given **with** and/or **without** 150 ml of water, is bioequivalent to the 4 mg Zofran tablets.
- The "*time of the sample in which the maximum measured plasma Ondansetron concentration occurred*" or t_{max} results from all three studies and across all treatments, suggest that there is a quicker and higher exposure to Ondansetron from Zydis tablets when given with water, as compared to Zydis without water or to Zofran tablets with water. This may be the reason for a higher incidence of adverse events in all subjects receiving Zydis with water.

◊ The Medical Reviewer should judge the observed results of up to a 50% higher incidence of adverse events within healthy subjects receiving Zydis with 150 ml of water, as compared to patients receiving Zofran with water or Zydis without water in the first Bioequivalence Study, Protocol No. 517/410. If this is concluded to be a concern, the following "Adverse Event" safety statement should be incorporated in the Adverse Events/Safety section of the label insert, so to make physicians and patients aware of possible side effects:

[redacted]

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmacologic Evaluation II has reviewed the information and data submitted with this NDA on July 1, 1997. Based upon an evaluation of the provided information and data it is concluded that:

1. The new freeze dry 4 mg and 8 mg tablet formulations of Ondansetron base, Zofran Zydis, are equivalent in extent of absorption (*i.e.* C_{max} and AUC_{∞}) to the reference formulation or respective marketed Zofran 4 mg and 8 mg tablets. Using recommended dosing instructions, the differences in the mean-time-to-peak-concentration (T_{max}) for Zydis 4 mg versus Zofran 4 mg and Zydis 8 mg versus Zofran 8 mg are 15 minutes and 3 minutes, respectively. If the differences in Tmax for the Zydis and Zofran tablet strengths are not determined to be clinically significant by the reviewing medical officer, these products can be considered bioequivalent.
2. Regarding the in-vitro dissolution information and data that has been provided in this NDA submission, it is felt that additional testing is required. This could be obtained post-approval and it is recommended that the sponsor contact the Agency to discuss the specifics of what is needed (*e.g.* appropriate media).
3. Currently, the FDA is attempting to standardize the content and presentation of the information that is to be given in the *Pharmacokinetics* portion of the *Clinical Pharmacology* section of the package insert. The *Pharmacokinetics* portion should present information as appropriate under the subheadings of *Absorption, Distribution, Metabolism,* and *Excretion.* Following this, there should be a section with the heading *Special Populations*, where pharmacokinetic information under the subheadings of *Geriatric, Pediatric, Gender, Race, Renal Insufficiency, Hepatic Insufficiency,* and *Drug-Drug Interactions* should be included. Where relevant information is lacking it should be so stated. Lastly, a table(s) with means (±SD) pharmacokinetic parameters determined under single and steady state conditions should be prepared, as appropriate. This table(s) should include bioavailability, peak concentration, time to peak, clearance, volume of distribution, half-life, and renal clearance for healthy subjects, and each special population including drug's intended target population, where data exists. Also, if appropriate a plot that illustrates drug plasma/serum concentration *vs.* time (*i.e.* different dosage strengths, comparison to a reference product) may be included.

4. The sponsor should incorporate the following adverse-event/safety statement within the Adverse Events/Safety section of the package insert, if the reviewing medical officer concurs.

[redacted]

/S/

Alfredo R. Sancho, Ph.D.
Pharmacologist/Pharmacokinetic Reviewer
Gastrointestinal and Coagulation Section
Radiopharmaceuticals and Medical Imaging Section
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

/S/ 6/29/98

John Hunt
Team Leader, Pharmacokineticist
Gastrointestinal and Coagulation Section
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Cc: HFD-160 NDA 20-781 (1x); DIV.FILE (1x); JOHNSON (1X); SANCHO (1X); HUNT (1X)
HFD-870 JHUNT (1x); MLCHEN (1x)
HFD-850 LLESKO
CDR Attn.: Barbara Murphy

Enclosures: [Click here and type number]

Attachments

APPEARS THIS WAY
ON ORIGINAL

Drug Name: Zofran (Ondansetron) Zydis Tablets	Study Type: Pilot Pharmacokinetic Study	Study No.: C/94/010 Report No.: GCP/94/010	Volume: 10/15 Pages: 46-237

Title: A pilot study to investigate the release and absorption of Ondansetron from 8 mg Zydis formulation.

Clinical Investigator:

Clinical Site:

Analytical Investigator:

Analytical Site: Biokinetic Unit, Glaxo Evreux France

Study Date/s: 06 June to 28 June 1994

Analysis Date/s: 22 June to 5 July 1994

Objectives

- To demonstrate that the use of the Ondansetron base rather than the hydrochloride dihydrate salt did not affect the dissolution and rate of absorption of Ondansetron from the Zydis formulation.
- To evaluate the effect of dosing Zydis without water.
- To provide data for a power statement for future definitive bioequivalence studies.

Study Design

Single Dose: *(Each subject received a single dose -of the same treatment- on three separate occasions according to a random code)*

- 8 mg Zofran tablet with 150 ml of water.
- 8mg Zydis tablet formulation with 150 ml of water for washdown.
- 8mg Zydis tablet formulation without water.

Details:

- Cross-over, open-label, randomized, three-way study.
- 72 hour washout interval between dosing occasion in the same volunteer.

Fasted: No food nor liquids from 24 hours prior to treatment

Pre-Dose Food Intake: 200 ml of water on rising

Post-Dose Fasting Period: No food nor liquid intake until 4 hours after treatment

Note/s: Volunteers will remain semi-recumbent for 2 hours after dosing.

Subjects: Six healthy human male volunteers of any ethnic origin.

Inclusion criteria:

- "Healthy" male volunteers.
- Between the ages of 18 and 50.
- Negative HBs antigen and HC antibody.
- Free from significant cardiac, pulmonary, gastrointestinal, hepatic, renal, hematological, neurological, and psychiatric diseases as determined by acquired medical history, physical examination, and screening laboratory results.
- Written and signed informed consent.

Exclusion criteria:

- Participants in another study within the previous 3 months.
- Blood donations of at least 450 ml within the previous 3 months.
- History of drug allergies.
- History of drug and/or alcohol abuse.
- Subjects who drink more than 4 units of alcohol per day.
- Smoking more than 15 cigarettes or 3 cigar/pipes per day.

Withdraw Criteria:

- Clinically significant adverse effects of the study drug.
- Clinically significant abnormalities of laboratory test results.
- Clinically significant intercurrent illness.
- Subjects not wishing to continue with the study for any reason.

Group:	Species:	Total No.:
Healthy subjects	Homo sapiens sapiens	6

Males:	Weight:	Age:	Females:	Weight:	Age:
6	N/A	18 - 40	0	N/A	N/A

Group:	Dose:	Dosage Form:	Strength:	Lot No.:
Treatment A	8 mg	Zofran tablets	8 mg Ondansetron	B0293MD

Group:	Dose:	Dosage Form:	Strength:	Lot No.:

Treatment B	8 mg	Zydis tablets	8 mg Ondansetron	1096-4AFD077*

*NOT in marketable form.

Group:	Dose:	Dosage Form:	Strength:	Lot No.:
Treatment C	8 mg	Zydis tablets	8 mg Ondansetron	1096-4AFD077*

*NOT in marketable form.

Safety

Prior to each treatment, each of the volunteers had the following procedures done: a 12-lead ECG, blood pressure, pulse rate, and laboratory test (including hematology, biochemistry, and urinalysis). Study Stopping Rules were not considered applicable in this protocol.

PK/PD Sampling Time Points

Body Fluids:

Blood: Hematology and biochemistry pre and post study analysis. Blood samples of 7 ml were taken from each subject prior to dosing and at 20, 40, 60, 80, 100 minutes, and at 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, and 10 hours post-dose. Total blood loss due to sampling will be 380 ml per patient.

Urine: Urinalysis pre and post study.

Note/s: Blood samples of 7 ml will be centrifuged (1500 G for 10 minutes) and at least 2 ml of plasma will be used for the assays. The plasma samples were placed in individually labeled polypropylene vials and kept in dry ice (-18°C) during transportation to Glaxo France, where they were assayed.

PK Analytical Method/s

Purpose/s: PK parameters were derived from each subject from the plasma Ondansetron concentration. The maximum measured plasma Ondansetron concentration (C_{max}); the time of the sample in which Cmax was measured (t_{max}); the terminal elimination rate constant for Ondansetron in plasma (λ_2) and the corresponding terminal plasma half-life ($t_{1/2}$); and, the area of the curve of plasma Ondansetron concentration versus time, extrapolated to infinite time (AUC_∞).

Method/s: Ondansetron plasma concentrations were determined using [redacted] The limit of quantification from a 1 ml plasma sample was [redacted]

Pharmacokinetic Parameter Analysis: The terminal elimination rate constant was determined by linear least regression using logarithmically transformed points in the terminal phase. The number of points included in the terminal phase were determined by inspection of a log-linear plot of Ondansetron concentration against time. All analyses were performed using PCNONLIN, Model 202, Version 4.0. No formal statistical analysis was carried out.

Results

1. Demographic data (Expressed in means and/or ranges):

Group	Gender	No.	Age (yr.)	Weight (kg)	Alcohol Intake/week	Smoking status
"Healthy" Homo sapiens sapiens	Males	6	31.2 28 - 34	79.0 67.7 - 88.6	15.2 alcohol-units	1

2. Dietary Intake: No food nor water from at least 24 hrs (over-night) prior to dosing and no food until 4 hrs after dosing. Subjects were allowed 200 ml of water on rising.

3. Body Fluid Concentrations:

   A. Plasma

Group	Dosage	C_{max} (ng/ml)	AUC_{∞} (ng.h/ml)	t_{max} (hr)	$t_{1/2}$ (hr)
Trt. A	8 mg Zofran Tablet	24.3	125.1	1.3	3.37
Trt. B	8 mg Zydis w/water	29.5	160.4	1.2	3.94
Trt. C	8 mg Zydis w/o water	23.8	152.0	1.6	3.65

   B. Urine: No data was provided by the sponsor in the submission.

4. Safety

No adverse events related to the drug presented themselves during the study. No subjects were withdrawn during the study. One subject had a "panic-attack" and reported as a adverse effect during the treatment regimen with Zofran tablet and water.

Discussion

Ondansetron, based on the limited safety results submitted, seems to be well tolerated by the subjects in which it was tested (healthy adult human males under fasting conditions and no special diet).

The sponsor provided adequate information on the assay system used and the quality control procedures followed to asses sensitivity and reproducibility of Ondansetron plasma concentration measurements. According to the information submitted by the sponsor, the blood sampling time deviations were within ±1 minute of the prescribed time point.

The sponsor did not submit the pharmacokinetic parameter AUC_{0-t} (Area Under the Curve) for 0 to the final measurement time point. The AUC submitted was an extrapolated value of 0 to infinity.

The results presented in this pilot study tend to suggest that a higher exposure to Ondansetron occurs from the Zydis tablet without water formulation as compared to the Zofran tablet with water, when the AUC_∞ parameter is compared (152.0 ng.hr/ml and 125.1 ng.hr/ml, respectively). The increased Ondansetron exposure from the Zydis tablet may be due to an increased rate of absorption from this tablet as compared to the conventional Zofran tablet. This increased exposure to Ondansetron from Zydis tablets is further enhanced with the presence of co-administered water, as shown by the comparison of the AUC_∞ parameter (160.1 ng.hr/ml versus 125.1 ng.hr/ml, and 152.0 ng.hr/ml). The presence of water co-administered with Zydis is also noted by the slight decrease of t_{max} over that of Zofran and Zydis without water (1.2 hr versus 1.3 hr, and 1.6 hr). There is also a slightly greater and more variable "lag-time" with the Zydis without water as compared to the Zydis with water when comparing the individual "plasma-concentration-versus-time" profiles shown in Figures 3-4, volume 10, pages 75-76. This increased "lag-time" and variability of exposure can be attributed to the Ondansetron plasma concentration measurements of two out of six subjects involved in this pilot study, that is subjects 3 and 5.

Great intersubject variability was evident when not only observing the plot of each individual subject data (*e.g.* Ondansetron Concentration in Plasma (ng/ml) versus Time (hr) shown in appendix 6, volume 10 of this submission), but also by comparing the means (and their respective ±SD and their respective ranges) of the calculated pharmacokinetic parameters across each of the three treatment groups. Some subjects demonstrated an increased AUC, hence maybe a lower elimination rate constant, while other subjects had greater peak plasma concentrations. Furthermore, while all subjects reached t_{max} within the first two hours (*i.e.* 1.2, 1.3, and 1.6 hr respectively) after dosing, the calculated AUC_∞ for each individual varied greatly (*i.e.* 125.1, 152.0, and 160.1 ng.hr/ml respectively), that is up to a 25% difference between the highest and lowest AUC_∞ mean value.

Reviewer's Conclusions

⇒ Ondansetron seems to be well tolerated among healthy subjects under fasting conditions and without special diets, for there were no reported adverse events.

⇒ The t_{max} for Ondansetron is slightly longer when Zydis tablet is given without water, than when given with water (1.3, 1.2, and 1.6 hr, respectively).

⇒ In this pilot study the Zydis tablet formulation is 21 to 28% more bioavailable as compared to Zofran tablet formulation (125, 160, and 152 ng.hr/ml, respectively).

⇒ There seems to be higher intersubject variability in Ondansetron absorption and elimination when given in the Zydis tablet without water formulation as compared to Zofran tablet with water formulation. This intersubject variability is further increased with the co-administration of Zydis with water.

⇒ It is not clear if the Zydis tablet formulations used in this pilot study is the to-be-marketed formulation.

Drug Name: Zofran (Ondansetron) Zydis Tablets	Study Type: Bioequivalence Pivotal	Study No.: 517/410 Report No.: UCP/95/053	Volume 10/15 Pages: 239-297

Title: An Evaluation of Relative Bioavailability of Ondansetron from an 8 mg Zydis formulation and an 8 mg Zofran tablet. (Sponsor's Report UCP/95/053)

Clinical Investigator: [redacted]

Analytical Investigator:

Clinical Site: [redacted]

Analytical Site: Clinical Pharmacology Department, Glaxo Inc., Research Park, North Carolina, USA

Study Date/s: 11 Feb 95 to 11 Mar 95

Analysis Date/s: N/A

Objectives

- To assess bioavailability of Ondansetron 8 mg from a Zydis formulation taken without water relative to 8 mg conventional Zofran tablet.
- To assess the effect of water on bioavailability of Ondansetron from the Zydis formulation relative to Zydis without water.

Study Design

Single Dose: (one of the following per volunteer per occasion, on three separate occasions.)

- Treatment A - 8 mg Zofran tablet with 150 ml of water.
- Treatment B - 8mg Zydis tablet formulation without water.
- Treatment C - 8mg Zydis tablet formulation with 150 ml of water for washdown.

Details:

- Three-way crossover, open-label, randomized, single centre study.
- 3 - 7 days washout interval between dosing occasion in the same volunteer.

Fasted: 8hrs prior to dosing	Pre-Dose Food Intake: water	Post-Dose Fasting Period: N/A
Food Study: N/A	FDA High Fat Breakfast: N/A	Others: No food nor liquids until after 5 hrs post-dosing

Subjects: 24 human healthy subjects of any ethnic origin.

Inclusion Criteria:

- Healthy subjects (male or female volunteers).
- Aged between 18 and 40 years.
- Free from significant health problems as determined by history, physical examination, and laboratory screens.
- Available to complete the study.
- Negative hepatitis B and HIV tests.
- Give written, informed consent.

Exclusion Criteria:

- Those who have participated in a study within the previous 30 days.
- Those who have donated 450 ml blood or more within the previous 3 months.
- Those who have a history of drug allergy which contraindicates their participation in the study.
- Those who have received a regular course of medication, including over-the-counter preparations and birth control medications, during the seven days prior to the initial drug administration or who will have difficulty of abstaining from any medication until they are discharged from the study.
- Those with a positive urine screen for drugs of abuse, or history of or current abuse of any drug substitute.
- Weigh outside 15% of ideal body weight as indicated in the standard height and weight tables.
- Those who have not abstained from tabacco use for at least two months prior to enrollment in the study and who will have difficulty abstaining from tabacco use for the duration of the study.
- Those with a history of clinically significant alcohol or drug abuse as patterns of alcohol intake consistent with disruption of normal function in society.

Withdraw Criteria:

- No withdraw criteria were included in either the protocol nor in the Report of the data submitted in this submission.

Group:	Species:	Total No.:
Healthy subjects	Homo sapiens sapiens	24

Males:	Weight:	Age (yr.):	Females:	Weight:	Age (yr.):
12	N/A	18 - 40 years	12	N/A	18 - 40 years

The clinical supplies used in this study were supplied by Glaxo Canada Inc. and were of the same grade as the marketable product. The supplies were distributed in each of the treatment groups as follows:

Group:	Dose:	Dosage Form:	Strength:	Expiration Date:	Lot No.:
Treatment A	8 mg	Zofran tablet	8 mg Ondansetron	30 Nov. 96	B0293MD

Group:	Dose:	Dosage Form:	Strength:	Expiration Date:	Lot No.:
Treatment B	8 mg	Zydis tablet	8 mg Ondansetron	03 Nov. 96	94J020C

Group:	Dose:	Dosage Form:	Strength:	Expiration Date:	Lot No.:
Treatment C	8 mg	Zydis tablet	8 mg Ondansetron	03 Nov. 96	94J020C

Safety

Prior to each treatment, each of the subjects had the following procedures done: a 12-lead ECG, blood pressure, oral temperature, respiratory rate, pulse rate, and laboratory test (including hematology, biochemistry, and urinalysis). Female subjects will also have a serum beta HCG pregnancy test. There were no "Study Stopping Rules" in this protocol.

PK/PD Sampling Time Points

Body Fluids:

Blood: Venipuncture using a red top Vacutainer with no anticoagulant was used to obtain 7 ml of blood at each sampling time point. Samples were collected from each subject prior to dosing and at 20, 40, 60 minutes and 1.5, 2, 2.5, 3, 4, 6, 7, 8, 10, 12, 16, and 24 hours after each treatment. (Standard meals will be provided at 5 hrs and between 10 and 12 hrs post-dosing.)

Urine: Standard Urinalysis testing was done on all urine samples collected from each subject.

Note/s: Blood samples used for pharmacokinetic analysis were allowed to stand at room temperature for 30 to 60 minutes to allow for clotting. Blood samples were centrifuged at 1500 G for 15 minutes. A minimum of 2 ml of serum was transferred to each polypropylene storage tube. Samples were stored in freezer set at -18 oC or lower until transferred to

PK Analytical Method/s

Purpose/s: To measure the level of Ondansetron present in each blood sample taken at distinct time points from each subject.

Method/s: Serum concentrations of Ondansetron was measured by [redacted] Inter-day precision based on quality control samples was ≤ 8.0% and inter-day accuracy ranged from 100% to 103% of nominal. Calibration curves resulted in correlation coefficients of ≥ 0.99 over the standard concentration range of [redacted]

Pharmacokinetic Parameter Analysis: The terminal elimination rate constant will be estimated by linear regression of logarithmically transformed concentration versus time data in the terminal phase. The number of points to be included in the terminal phase will be determined by inspection of a log-linear plot of Ondansetron concentration against time. The following parameters were derived for each subject from the serum Ondansetron concentration-time data:

- The maximum measured serum Ondansetron concentration (C_{max});
- The time of the sample in which Cmax was measured (t_{max});
- The terminal elimination rate constant for Ondansetron in serum (λ_z) and the corresponding terminal serum half-life ($t_{1/2}$); and,
- The area under the curve of serum Ondansetron concentration versus time, extrapolated to infinity (AUC_∞).

Results

1. Demographic data:

Group	No.	Gender		Age (yr.)	Height (cm)	Weight (kg)
Healthy	25	12-M & 13-F	*mean*	27	167.89	66.8
			range	18 - 38	61.0-70.1	52.4 - 83.7

The subjects involved in this study included 16 non-smokers, 9 former tobacco users, none were current users. The sponsor defines a 1 unit of Alcohol intake as a 1bottle (12 oz) of beer, or 1 glass (4 oz) of wine, or as 1 shot (1-1/2 oz) of liquor. In this study the alcohol consumption per week varied from 0 up to 6 units per week per subject, with a mean alcohol unit consumption of 2.

2. Dietary Intake: No food nor liquids from at least 8 hrs (over-night) prior to dosing and no food until 5 hrs after dosing. Subjects were allowed 200 ml of water at rising.

3. Body Fluid Concentrations:

B. Plasma

Group	Dosage	Cmax (*ng/ml*)	AUC_∞ (*ng.hr/ml*)	tmax (*hr*)	$t_{1/2}$ (*hr*)
Treatment A	8 mg Zofran w/ 150 ml of water	32.0 ±10.1	204 ±33.2	2.13 ±0.63	4.36 ±0.89
Treatment B	8 mg Zydis w/o water	31.8 ±9.4	204 ±33.6	2.08 ±0.52	3.89 ±0.93
Treatment C	8 mg Zydis w/ 150 ml of water	33.7 ±13.3	206 ±34.2	2.02 ±0.77	3.80 ±0.97

Safety

Although the sponsor states that there were no "serious" adverse effects, 16 of 24 subjects reported some level of adverse effect, such as headache, dizziness, and tiredness. In addition to these 16 subjects, one subjects (Subject #107: 34 year old Caucasian/white female, 129.4 lb., 65.0 cm, "small" body frame, "former" smoker, and an alcoholic intake of "1 unit per week") was withdrawn from the study due to severe "stomach ache", which was considered to be non-related to the drug given (8 mg Zydis tablet with 150 ml of water). This subject was replaced by another subject who was assigned the same random code.

The sponsor states that, overall no significant changes occurred in the laboratory values nor in the vital sign parameters used to monitor the subjects prior, during, and after each of the dosing treatments.

Discussion

A total of 16 adverse events were reported across all three treatments, out of a total of 25 subjects. The incidence of adverse events was similar between Treatment A (8 mg Zofran with 150 ml of water) and Treatment B (8 mg Zydis without water). While, five subjects reported adverse events during the treatment with Zofran, six subjects reported adverse events during the treatment with Zydis without water. A total of 12 subjects who received Treatment C (8 mg Zydis with 150 ml of water) reported adverse events. These adverse events, in all three treatments, were classified as "mild in nature" by the sponsor. The most frequent adverse event across all three treatments was headache which was reported by one subject during Treatment A, two subjects during Treatment B, and six subjects during Treatment C (8 mg Zydis with 150 ml of water).

No drug-related (as defined by the sponsor) adverse events were reported by more than one subject during Treatment A or Treatment B. During Treatment C (8 mg Zydis with 150 ml of water), the most frequently reported drug-related adverse event was headaches (4 subjects) followed by dizziness and tiredness (3 subjects each). The most serious adverse event was reported by Subject 7 (ID #107) who withdrew after the first dosage of Treatment C due to stomach ache.

One of the objectives of this study was to determine the bioavailability of Ondansetron 8 mg Zydis formulation taken without water (Treatment B) relative to Ondansetron 8 mg Zofran with 150 ml of water (Treatment A), both when administered orally to healthy adult, males and females, subjects. The geometric least squares mean ratio (B/A) between treatments B and A for AUC_{∞} is 1.03, with a 90% confidence interval (CI) of 0.99 to 1.08; for C_{max} the ratio is 1.03 with a 90% CI of 0.98 to 1.09. These results indicate that the two formulations are bioequivalent. The other objective of this study was to determine the bioavailability of Ondansetron 8 mg Zydis formulation taken with water (Treatment C) relative to Ondansetron 8 mg Zydis taken without water (Treatment B). The geometric least squares mean ratio (C/B) between treatments C and B for AUC_{∞} is 1.02 with a 90% CI of 0.97 to 1.07; for C_{max} it is 1.07 with a 90% CI of 1.02 to 1.14. These results indicate that co-administered water has no significant effect on the bioavailability of Ondansetron from Zydis formulation when taken with water relative to without water. The statistical analysis of the selected pharmacokinetic parameters (AUC_{∞}, C_{max}, t_{max}, and $t_{1/2}$) is summarized in the following table:

		Treatment A		Treatment B		Treatment C	
		8 mg Zofran tablet w/150ml of water	B/A	8 mg Zydis tablet w/o water	C/B	8 mg Zydis tablet w/150ml of water	C/A
AUC_∞ *ng.hr/ml*	*Mean*	204		204		206	
	Range	[redacted]		[redacted]		[redacted]	
	±SD	33.2		33.6		34.2	
	CV	71		72		74	
	95% CI	194 - 215		194 - 215		195 - 217	
	Mean Ratio		1.03		1.02		1.01
	90% CI		0.99-1.08		0.97-1.07		0.97-1.06
	p-value		*0.9966*		*0.8506*		*0.8507*
C_{max} *ng/ml*	*Mean*	32.0		31.8		33.7	
	Range	[redacted]		[redacted]		[redacted]	
	±SD	10.1		9.4		13.3	
	CV	30.1		28.5		33.2	
	95% CI	30.1-34.1		29.9-33.8		31.6-35.8	
	Mean Ratio		1.03		1.07		0.96
	90% CI		0.98-1.09		1.02-1.14		0.91-1.01
	p-value		*0.8769*		*0.1991*		*0.2583*
t_{max} *hr*	*Mean*	2.13		2.08		2.02	
	Range	[redacted]		[redacted]		[redacted]	
	±SD	0.63		0.52		0.77	
	CV	29.7		25.2		38.2	
	95% CI	1.0-4.0		1.8-2.3		1.8-2.3	
$t_{1/2}$ *hr*	*Mean*	4.36		3.89		3.80	
	Range	[redacted]		[redacted]		[redacted]	
	±SD	0.89		0.93		0.97	
	CV	20.1		23.3		24.8	
	95% CI	4.08-4.65		3.65-4.16		3.56-4.06	
	Mean Ratio		0.92		0.87		1.05
	90% CI		0.87-0.97		0.82-0.93		0.99-1.11
	p-value		*0.0186*		*0.6119*		*0.0049*

Treatment C (8 mg Zydis with 150 ml of water) when compared to the other two treatments (A and B), has a higher incidence of adverse events and a higher degree of intersubject variability or wider ranges for C_{max}, AUC and T_{max}, but a narrower range for $t_{1/2}$. Nevertheless all three treatments demonstrate bioequivalency as determined through the 2 one-sided test for C_{max}, AUC, t_{max}, and $t_{1/2}$.

Reviewer's Conclusions

⇒ The Ondansetron 8 mg Zydis tablets taken without water (Treatment B) or with water (Treatment C) are shown to be equivalent in C_{max} and AUC_{∞} compared to the approved Ondansetron 8 mg Zofran tablet taken with 150 ml of water (Treatment A). The difference in mean Tmax values for treatment B (Zydis without water) versus treatment A (Zofran with water) is 0.05 hr or 3 minutes. The difference in mean Tmax values for Treatment C (Zydis with water) versus treatment A (Zofran with water) is 0.11 hr or 6.6 minutes.

⇒ A total of 16 adverse events were reported across all three treatments, for a total of 25 subjects. No serious adverse events nor deaths occurred during the study. Drug-related adverse events, as defined by the sponsor, were headaches, dizziness, and tiredness. One subject withdrew (Subject #7, ID #107) due to stomach ache after the first dosage of Treatment C (8 mg Zydis with 150 ml of water), which was not considered by the sponsor to be drug-related.

⇒ Although all three treatments seem to be relatively well tolerated, it should be noted that Treatment C (8 mg Zydis with 150 ml of water) had twice as many adverse events reported (12) as compared to Treatments A or B (5 and 6, respectively). Furthermore, the only subject that was withdrawn from the study due to an adverse event (stomach ache) was after the first dosage of Treatment C.

⇒ When Treatment C (8 mg Zydis with 150 ml of water) is compared to either of the other two treatments (A or B), it has slightly higher AUC_{∞} mean value (206 ng.hr/ml), greater AUC_{∞} Standard Deviation (±74 ng.hr/ml), and an AUC_{∞} larger range ([redacted] ng.hr/ml). This same group also demonstrate a slightly higher C_{max} mean value (33.7 ng/ml) with a greater Standard Deviation (±13.3) and a larger range ([redacted] ng/ml). While the median for this treatment group is the same as for the other treatment groups, the arithmetic mean t_{max} is shorter (2.02 hr), the Standard Deviation is greater (0.77 hr) and the range is larger ([redacted] hr). Finally, the $t_{1/2}$ mean value is shorter (3.80 hr), its range is smaller ([redacted] hr), but its Standard Deviation is greater (0.97 hr).

⇒ Although the administration of 8 mg Zydis with 150 ml of water (Treatment C) seems to not have any significant effect on the bioavailability of Ondansetron as compared to Treatment B, there is a higher incidence of adverse events and higher degree of intersubject of variability within this treatment group.

Drug Name: Zofran (Ondansetron) Zydis Tablets	Study Type: Pivotal Bioequivalence Study II	Study No.: 032X-01 Report No.: JJB/96/001	Volume: 11/15 Pages: 297 - 499

Title: An Evaluation of Bioequivalency of the Ondansetron Zydis 4 mg Tablet and the Zofran 4 mg Tablet.

Clinical Investigator: [redacted] Analytical Investigator: [redacted]

Clinical Site: [redacted] Analytical Site: Nihon Gurakuso KK [Glaxo Japan], Ibaragi-ken, Japan

Study Date/s: 00 Dec. 1994 to 00 Feb. 1995 Analysis Date/s: 00 Dec. 1994 to 00 Feb. 1995

Objective

- To examine the bioequivalence of 4 mg tablets of GG032 (Zofran tablet, Ondansetron hydrochloride) and 4 mg troches of GG032X (Zydis tablet, Ondansetron base).

Study Design

Single Dose: *(Each subject received a single dose of each treatment on two separate occasions according to a random code.)*

- 4 mg Zofran tablet (GG032) with 150 ml of water.
- 4 mg Zydis tablet (GG032X) without water.

Details:

- Cross-over method (2 stages, 2 substances).
- Approximately 7 days washout interval between dosing occasion in the same volunteer.

Fasted: No food nor liquids from 21 hours prior to treatment

Pre-Dose Food intake: 200 ml of water on rising

Post-Dose Fasting Period: No food nor liquid intake until 4.5 hours after treatment

Note/s: *Subjects need to abstain from alcohol and smoking from 21 hours prior to treatment.*

Subjects:

Inclusion Criteria:

- "Healthy" male volunteers.
- Between the ages of 20 and 30.
- Written and signed informed consent.

Exclusion Criteria:

- Not included in the submission.

Withdraw Criteria:

- Not included in the submission.

Group:	Species:	Total No.:
Healthy subjects	Homo sapiens sapiens	30

Males:	Weight:	Age:	Females:	Weight:	Age:
30	N/A	20 - 30	N/A	N/A	N/A

Group:	Dose:	Dosage Form:	Strength:	Lot No.:
GG032 w/150 ml of water	4 mg	Zofran tablets	4 mg Ondansetron	4C152A

Group:	Dose:	Dosage Form:	Strength:	Lot No.:
GG032X w/o water	4 mg	Zydis tablets	4 mg Ondansetron	94J030B

Safety

Prior to each treatment, each of the subjects will have the following procedures done: laboratory tests (including hematology, urinalysis, and biochemistry), blood pressure, pulse rate, and body temperature.

PK/PD Sampling Time Points

Body Fluids:

Blood: A venoject heparin-treated vacuum tube for collecting blood is to be used to collect 10 ml of whole blood prior to administration, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours after treatment, for a total of 12 time points.

Urine: Pre and Post study collection and urinalysis.

PK Analytical Method/s

Purpose/s: To obtain the plasma Ondansetron concentrations at each time point so to calculate the desired PK parameters.

Method/s:

Pharmacokinetic Parameter Analysis: Analysis of variance (α = 0.05-0.10) and degree of accuracy (minimum detected difference Δ, power of test 1-β, confidence interval δ, number of examples required in each group n) will be investigated using C_{max} and AUC in accordance with the method described by Ejima *et al.* In "Analysis in relation to bioequivalence studies." The pharmacokinetic parameters to be calculated will be the maximum plasma concentration (C_{max}), the area under the plasma concentration-time curve (AUC), the mean retention time (MRT), and any changes in plasma concentration.

Results

1. Demographic data:

Group	Gender	No.	Age (yr.)	Height (cm)	Weight (kg)
"Healthy"	Males	30	24.5	171.1	64.4
Homo sapiens sapiens			20 - 30	162.1 - 187.2	52.5 - 95.0

2. Dietary Intake: No food nor water from at least 21 hours (over-night) prior to dosing and no food until 4.5 hours after dosing. Subjects allowed 200 ml of water on rising.

3. Body Fluid Concentrations:

   A. Plasma

Group	C_{max} *(ng/ml)*	AUC_{0-t} *(ng/ml-hr)*	t_{max} *(hr)*	$t_{1/2}$ *(hr)*
4 mg Zofran tablet (GG032)	12.59 ±5.83	88.64 ±55.56	2.16 ±0.71	4.31 ±2.17
4 mg Zydis tablet (GG302X)	13.30 ±5.74	89.61 ±37.34	2.41 ±0.82	4.49 ±1.86

   B. Urine: Collected urine was used to run urinalysis on each of the subjects.

4. Safety

No clinical symptoms were observed during the study. Results from laboratory tests demonstrated a slightly elevated GPT in two subjects (Subjects 5 and 6), 24 hours after administration in stage 1 (GG032, 4 mg Zofran tablet). Slightly elevated uric acid levels were observed in one subject, 24 hours after administration in stage 2 (GG032X, 4 mg Zydis tablet). Subject #13 drop-out of the study during stage 2 (GG032X, 4 mg Zydis tablet) due to influenza.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-781

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 20-781 SUPPL # N/A

Trade Name Zofran ODT Orally Disintegrating Tablets **Generic Name** (ondansetron)

Applicant Name GlaxoWellcome **HFD-** 180

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /_X_/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_X_/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /___/ NO /_X_/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /__/ NO /_x_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /__/ NO /_x_/

If yes, NDA # _____ Drug Name_____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /__/ NO /__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

APPEARS THIS WAY
ON ORIGINAL

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-007 Zofran (ondansetron HCl) Injection

NDA # 20-103 Zofran (ondansetron HCl) Tablets

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /__/ NO /__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /X/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

APPEARS THIS WAY
ON ORIGINAL

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

APPEARS THIS WAY
ON ORIGINAL

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

APPEARS THIS WAY
ON ORIGINAL

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # ____ YES /___/ NO /___/ Explain: ____

Investigation #2

IND # ____ YES /___/ NO /___/ Explain: ____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

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Investigation #2

YES /___/ Explain _____ | NO /___/ Explain _____

_____ | _____

_____ | _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

/S/ 1/23/99

Signature Date

Title: Supervisory Consumer Safety Officer

/S/ 1-27-99

Signature of Division Director Date

APPEARS THIS WAY
ON ORIGINAL

cc: Original NDA Division File HFD-85 Mary Ann Holovac

NDA 20-781

PATENT INFORMATION
for
ZOFRAN® (ondansetron) Zydis® Tablet

Product of
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	ZOFRAN® Zydis® Tablet
Active Ingredient:	Ondansetron
Patent Number:	5,578,628
Expiration Date:	June 24, 2006 (GATT Extended - a Certificate of Correction has been filed with the USPTO to correct the expiration date listed on the face of this patent)
Type of Patent:	Method of Use in treating nausea and vomiting
Name of Patent Owner:	GLAXO WELLCOME Inc.
U.S. Agent:	David J. Levy, Ph.D. Patent Counsel Glaxo Wellcome Inc. 5 Moore Drive P.O. Box 13398 Research Triangle Park, North Carolina 27709

The undersigned declares that Patent No. 5,578,628 covers the method of use of ondansetron in treating nausea and vomiting. This product is the subject of this application for which approval is being sought.

Date: May 20, 1997

By: Robert T. Hrubiec

Robert T. Hrubiec, Ph.D.
Registered Patent Agent
Glaxo Wellcome Inc.

NDA 20-781

PATENT INFORMATION
for
ZOFRAN® (ondansetron) Zydis® Tablet

Product of
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	ZOFRAN® Zydis® Tablet
Active Ingredient:	Ondansetron
Patent Number:	4,695,578
Expiration Date:	June 25, 2005
Type of Patent:	Drug Substance, Drug Product, and Method of Use
Name of Patent Owner:	GLAXO WELLCOME Inc.
U.S. Agent:	David J. Levy, Ph.D. Patent Counsel Glaxo Wellcome Inc. 5 Moore Drive P.O. Box 13398 Research Triangle Park, North Carolina 27709

The undersigned declares that Patent No. 4,695,578 covers the formulation, composition and/or method of use of ondansetron in treating nausea and vomiting. This product is the subject of this application for which approval is being sought.

Date: May 20, 1997

By: Robert T Hrubiec
Robert T. Hrubiec, Ph.D.
Registered Patent Agent
Glaxo Wellcome Inc.

NDA 20-781

PATENT INFORMATION
for
ZOFRAN® (ondansetron) Zydis® Tablet

Product of
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	ZOFRAN® Zydis® Tablet
Active Ingredient:	Ondansetron
Patent Number:	4,753,789
Expiration Date:	June 24, 2006
Type of Patent:	Method of Use - Relief of nausea and vomiting
Name of Patent Owner:	GLAXO WELLCOME Inc.
U.S. Agent:	David J. Levy, Ph.D. Patent Counsel Glaxo Wellcome Inc. 5 Moore Drive P.O. Box 13398 Research Triangle Park, North Carolina 27709

The undersigned declares that Patent No. 4,753,789 covers the method of using ondansetron in treating nausea and vomiting. This product is the subject of this application for which approval is being sought.

Date: May 20, 1997

By: Robert T. Hrubiec

Robert T. Hrubiec, Ph.D.
Registered Patent Agent
Glaxo Wellcome Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-781

CORRESPONDENCE

MEMORANDUM OF MEETING MINUTES

Meeting Date: August 20, 1997
Time: 10:00 am - 10:30 am
Location: Conference Room 6B-45

Application: NDA 20-781
Zofran (ondansetron) Zydis Tablets

Type of Meeting: Filing

Meeting Chair: Kati Johnson, Supervisor, Project Management Staff

Meeting Recorder: Kati Johnson

FDA Attendees, titles, and Office/Division:

Dr. Robert Prizont, Acting GI Team Leader
Dr. Hugo Gallo-Torres, Medical Reviewer
Dr. Jasti Choudary, Pharmacology Team Leader
Dr. Gerald Young, Pharmacology Reviewer
Dr. Lydia Kaus, Biopharmaceutics Team Leader

Background:
Zofran is available in an injection formulation for the prevention of chemotherapy induced emesis and for the prevention of postoperative nausea and vomiting. Zofran is available orally as tablet and solution formulations for these indications, and is also approved for the prevention of radiation induced emesis. The firm has submitted this application to market an oral (freeze-dried) tablet which rapidly disintegrates when placed on top of the tongue. Demonstration of safety and efficacy will be based on bioequivalence to the currently approved 4 and 8 mg oral tablets.

Meeting Objectives:

1. Determine whether the application will be filed.
2. Determine whether any additional information should be requested from the firm.

Discussion Points (bullet format):

1. Clinical-Although the firm submitted results from a clinical study conducted in Japan (comparing efficacy between the approved tablet and the proposed Zydis formulation), it is not the basis for approval, nor do they plan to mention the study in the proposed package insert. Dr. Gallo-Torres, reviewing Medical Officer, stated that he would probably not review the study unless it was deemed necessary by the Biopharmaceutics reviewer.

2. Pharmacology- There are preclinical study reports which will be reviewed.

3. Chemistry-The application appears reviewable. Two issues which were raised involve the firm's request for a waiver of the requirement under 21 CFR 206.7(b)(1) to imprint the tablet, and the acceptability of some wording contained in the permits submitted to address the environmental assessment.

   With regard to the request for a waiver with regard to imprinting the tablet, it is the firm's position that technical difficulties, among other things, does not make it feasible to do. In a Memorandum dated July 11, 1997 from Steven Koepke, PhD, Deputy Division Director, Division of New Drug Chemistry II, to Eric Sheinin, PhD, Director, Office of New Drug Chemistry, it was recommended that, for approval, the firm must provide a Phase 4 commitment to [redacted] A letter will be drafted which informs the sponsor of this policy.

4. Biopharmaceutics:

   The firm has included bioequivalence studies to both of the currently approved 4 and 8 mg tablets, both with and without concomitant water. The biopharmaceutics technical section of the application appears reviewable.

Decisions (agreements) reached:

The application will be filed. The PDUFA goal date is July 2, 1998. No further team meetings will be convened unless requested by one of the reviewers.

Minutes Preparer: /S/ 9/2/97

cc: Original
HFD-/Div. Files
HFD-/Meeting Minutes files
HFD-/CSO
HFD-/meeting attendees
Drafted by:KJohnson 8/21/97
Initialed by: Hgallo-Torres 8/21/97
J.Choudary 8/21/97
L. Kaus8/21/97
R. Frankewich 8/22/97
MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

CSO /S/

NDA 20-781

GlaxoWellcome Inc.
Attention: Kimberley Jessup-Crippen
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

AUG 11 1998

Dear Ms. Jessup-Crippen:

We acknowledge receipt on July 27, 1998 of your July 24, 1998 resubmission to your new drug application (NDA) for Zofran (ondansetron) Orally Disintegrating Tablets.

This resubmission contains additional chemistry, manufacturing and controls information submitted in response to our July 1, 1998 action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is January 27, 1999.

If you have any questions, contact me at (301) 443-0487.

Sincerely,

/S/ 8/11/98

Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20-781
HFD-180/Div. Files
HFD-180/K.Johnson
HFD-180/Frankewich
DISTRICT OFFICE

APPEARS THIS WAY
ON ORIGINAL

Drafted by: KJ/August 11, 1998
filename:c:\wpfiles\cso\n\20781.doc
ACKNOWLEDGEMENT (AC)

Redacted 4

pages of trade

secret and/or

confidential

commercial

information

NDA 20-781

GlaxoWellcome Inc.
Attention: George Phillips, Pharm.D.
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

JUL 11 1997

Dear Dr. Phillips:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Zofran (ondansetron) Zydis Tablets

Therapeutic Classification: Standard

Date of Application: July 1, 1997

Date of Receipt: July 2, 1997

Our Reference Number: 20-781

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 30, 1997 in accordance with 21 CFR 314.101(a).

If you have any questions, please contact me at (301) 443-0487.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

cc:
Original NDA 20-781
HFD-180/Div. Files
HFD-180/CSO/K.Johnson
DISTRICT OFFICE
Drafted by: kj/July 11, 1997
c:\wpfiles\cso\n\20781707.0kjk
ACKNOWLEDGEMENT (AC)

Sincerely yours,

/S/ 7/11/97

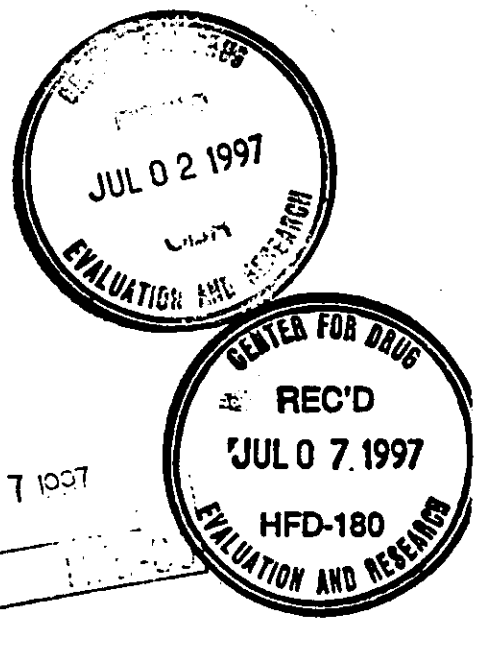
Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Debarment Statement on Page 3.

GlaxoWellcome

July 1, 1997

APPEARS THIS WAY ON ORIGINAL



Lilia Talarico, M.D., Acting Division 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
HFD-180, PKLN, 6B-45
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-781; Zofran® Zydis® Tablet
Original Application

Dear Dr. Talarico:

Pursuant to Section 505(b) of the Food, Drug, and Cosmetic Act, Glaxo Wellcome is submitting a New Drug Application providing for Zofran® (ondansetron) Zydis® Tablets, 4mg and 8mg.

Zofran Zydis Tablets were developed as an oral dosing alternative for the currently approved and marketed formulations of Zofran. Zofran Zydis Tablets are a palatable, freeze-dried, orally administered presentation of Ondansetron which disperses rapidly on the tongue and does not require water to aid dissolution or swallowing.

The information provided in this New Drug Application for Zofran Zydis Tablets includes preclinical, human bioequivalence and pharmacokinetic, and chemistry, manufacturing and controls data. A report of a foreign (Japanese) clinical study investigating the relative bioavailability of Zofran Zydis Tablets compared to conventional Zofran Tablets is also provided as supplemental information.

Although this submission is based on the clinical pharmacokinetics and bioavailability of Zofran Zydis Tablets compared to conventional Zofran Tablets, one clinical efficacy study was undertaken in Europe. A copy of the final study report and protocol is being provided for informational purposes. All other documentation generated from this study is on file at Glaxo Wellcome. Please note that although supporting efficacy was demonstrated, Glaxo Wellcome is not requesting any specific labeling statements based on this study.

Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 248 2100

The data from the clinical pharmacokinetic, bioavailability, and supportive clinical trial indicate that the 4 mg and 8 mg Zofran Zydis Tablet formulations are bioequivalent to equal strengths of the conventional Zofran Tablet and support the interchangeable use of these formulations for the management of chemotherapy-induced emesis, radiotherapy-induced emesis, or the prevention of postoperative nausea and/or vomiting. In addition, no new or unexpected adverse events associated with the use of Zofran Zydis Tablets were observed.

Due to its low solubility in saliva, Ondansetron base, in lieu of Ondansetron hydrochloride dihydrate, as found in the currently marketed forms of Zofran, will be employed in the formulation for Zofran Zydis Tablets. Thus, the unpleasant taste of the drug substance may be avoided. The manufacture of the drug substance for Zofran Zydis Tablets is identical to that currently approved for Zofran Injection and Zofran Tablet, up through production of intermediate grade Ondansetron. Zofran Zydis Tablets are then formed by freeze-drying an [redacted] of Ondansetron base in combination with various commonly used excipients.

Stability studies are in progress on three batches each of Zofran Zydis Tablets 4 mg and 8 mg. The data generated on Zofran Zydis Tablet units packed in double foil blisters and stored for up to 18 months at 2°C/Ambient RH and 30°C/60% RH show excellent physical and chemical stability. No significant changes in appearance, Ondansetron content, Ondansetron related impurities, dispersion time and dissolution have been observed at all conditions and timepoints studied. Statistical analyses of the Ondansetron content, total impurities and dissolution predict a shelf-life to support the proposed shelf-life of 24 months when product is stored between 2°C and 30°C.

Due to the manufacturing process employed and the unique chemical and physical characteristics of the Zofran Zydis Tablet formulation, tablet imprinting or engraving is not possible. Glaxo Wellcome requests a waiver from the final rule on imprinting of solid oral dosage forms (21 CFR 206.7(b)1, based upon the following:

- The dose characteristics require that it remains in its blister pack until just before administration. The blister foil is printed with full labeling details together with batch identification and expiry date.

- The pack size will be small and individual blisters will be separable to allow the use in a "daily reminder" container system.

- Zydis is the exclusive technology of [redacted] id is only manufactured at one site worldwide. Patent protection and the specialized nature of the process are expected to preserve that exclusivity for the foreseeable future.

Correspondence regarding the use of Ondansetron base in lieu of Ondansetron hydrochloride dihydrate, as well as information regarding the physical and chemical characteristics of Zofran Zydis Tablets supporting this waiver request was previously submitted to IND [redacted] on September 27, 1995, and is also addressed in the Chemistry, Manufacturing, and Controls section of this NDA.

Glaxo Wellcome certifies that it did not and will not use in any capacity the service of any person debarred under section 306(a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

In compliance with the requirements set forth in 21 CFR 314.50(d)(1)(v), a field copy of the Chemistry, Manufacturing, and Controls section of this application, along with a copy of the FDA form 356h and the Overall NDA Summary Volume for this application, is being provided to:

Food and Drug Administration
HFR-SE 150
60 Eighth Street, NE
Atlanta, GA 30309
Attn: Roger E. Kline

and

Division of Emergency & Investigational Operations
HFC-132, Office 1364
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions regarding this application please contact me at 919-483-4468.

Sincerely,

George C Phillips

George C. Phillips, Pharm.D.
Product Director
Regulatory Affairs

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