

LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

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February 5, 2004

OVERNIGHT COURIER 2/5/04

Division of Dockets Management
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Citizen Petition

Dear Sir or Madam:

The undersigned submits this petition, in quadruplicate, pursuant to section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act and in accordance with 21 CFR 10.30 on behalf of a client requesting the Commissioner of the Food and Drug Administration to declare that the drug products, Ondansetron Orally Disintegrating Tablets 16 mg and 24 mg are suitable for consideration in an abbreviated new drug application (ANDA).

A. Action Requested

The petitioner requests that the Commissioner of the Food and Drug Administration declare that Ondansetron Orally Disintegrating Tablets 16 mg and 24 mg are suitable for submission in an ANDA. The listed reference drug product upon which this petition is based is Zofran ODT® Orally Disintegrating Tablets (ondansetron), 8 mg (also available in a 4 mg strength). Therefore, the petitioner seeks a change in strength (from the currently approved 4 mg and 8 mg orally disintegrating tablets to include 16 mg and 24 mg strengths of the orally disintegrating tablets) from that of the listed drug product.

B. Statement of Grounds

The reference listed drug (RLD) product (Zofran ODT®) is currently available in approved tablet strengths of 4 mg and 8 mg containing ondansetron. A copy of the listing from the *Approved Drug Product with Therapeutic Equivalence Evaluations* 23rd edition is included in Attachment 1 (page 3-271). The proposed drug product represents an orally disintegrating tablet that will contain higher strengths of the drug (16 mg and 24 mg). These higher strengths are, however, consistent with and clearly contemplated in the currently approved RLD product's labeling and will provide both greater flexibility for the physician in providing a patient with the required dose in a single tablet and will represent a more convenient single-tablet dosage unit to provide the specific dose prescribed by the physician for an individual patient. The petition is thus seeking a change in strength (from the approved 4 mg and 8 mg tablet products to include 16 mg and 24 mg strengths) from that of the reference-listed drug.

2004P-0056

CP1

The RLD product's labeling provides for single doses of 16 mg for treatment of Postoperative Nausea and Vomiting in the dosage and administration section of the labeling as indicated below:

"The recommended dosage is 16 mg given as two 8-mg Zofran Tablets or **two 8-mg Zofran ODT tablets** or 20 mL Zofran Oral Solution 1 hour before the induction of anesthesia."

The RLD product's labeling also provides for single doses of 24 mg for the Prevention of Nausea and Vomiting Associated with Highly Emetogenic Cancer Chemotherapy in the dosage and administration section of the labeling as indicated below:

"The recommended adult dosage of Zofran is a single **24 mg** tablet administered 30 minutes before the start of single-day highly emetogenic chemotherapy..."

Therefore, the petitioner is seeking changes in strength from the RLD drug product to provide the patient and physician with a more convenient single dosage unit (orally disintegrating tablet) to provide a dose that is consistent with single doses clearly contemplated in the approved labeling of the RLD. The goal being to reduce the number of tablets a patient would need to take for a single dose. This will improve patient convenience, compliance and make it easier to achieve the required dose for those patients for whom a dose of 16 mg or 24 mg of the orally disintegrating formulation was found appropriate by the prescribing physician.

Copies of labeling of the reference listed drug product upon which this petition is based and draft labeling for the proposed product are included in Attachment 2 and Attachment 3, respectively. Please note that the draft labeling for the proposed product will be revised to include the inactive ingredients and a complete "How Supplied" section when the ANDA is submitted. The proposed labeling is the "same as" the approved RLD labeling with the exception of changes allowed because the manufacturer of the generic product differs from that of the RLD and in the Description section and How Supplied section (when included which will list the additional available strengths [16 mg and 24 mg] sought by this petition). There are no changes in the indications or dosage and administration sections necessary, as the approved labeling of the RLD already clearly contemplates and explicitly states the use of the proposed dosage strengths.

Because this petition requests only a change in strength from the listed drug, there is no requirement to request a waiver from the conduct of pediatric studies in accord with the Pediatric Research Equity Act of 2003.

Therefore, the petitioner requests that the Commissioner find that a change in strength from a 4 mg and 8 mg orally disintegrating tablets to include 16 mg and 24 mg strength tablets for this product raises no questions of safety or effectiveness, and the Agency should then approve the petition.

C. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR 25.31.

D. Economic Impact

The petitioner does not believe that this is applicable in this case, but will agree to provide such an analysis if requested by the Agency.

E. Certification

The undersigned certifies that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,



Robert. W. Pollock *PK*
Vice President
Lachman Consultant Services, Inc.
1600 Stewart Avenue
Westbury, New York 11590

RWP/pk/i

- Attachments: 1. Page 3-271 of the Approved Drug Product with Therapeutic Equivalence Evaluations, 23rd Edition
2. Labeling for Zofran®
3. Labeling for Ondansetron

cc: Emily Thomas (OGD)

S21P4036

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 1

PRESCRIPTION DRUG PRODUCT LIST

3-271

OLANZAPINE

TABLET, ORALLY DISINTEGRATING; ORAL
ZYPREXA ZYDIS
LILLY

10MG

15MG

+ 20MG

N21086 002
APR 06, 2000
N21086 003
APR 06, 2000
N21086 004
APR 06, 2000

OMEPRAZOLE

CAPSULE, DELAYED REL PELLETS; ORAL

OMEPRAZOLE

ANDRX PHARMS 40MG

EON 10MG

20MG

IMPAX LABS 10MG

20MG

KREMERS URBAN DEV 10MG

20MG

PRIOSEC

ASTRAZENECA 10MG

+ 20MG

+ 40MG

N75347 003
NOV 16, 2001
N75791 001
DEC 23, 2002
N75791 002
DEC 23, 2002
N75785 001
NOV 08, 2002
N75785 002
NOV 08, 2002
N75410 001
NOV 01, 2002
N75410 002
NOV 01, 2002
N19810 003
OCT 05, 1995
N19810 001
SEP 14, 1989
N19810 002
JAN 15, 1998

OLMESARTAN MEDOXOMIL

TABLET; ORAL
BENICAR
SANKYO

5MG

20MG

+ 40MG

N21286 001
APR 25, 2002
N21286 003
APR 25, 2002
N21286 004
APR 25, 2002

OLOPATADINE HYDROCHLORIDE

SOLUTION/DROPS; OPHTHALMIC
PATANOL

+ ALCON EQ 0.1% BASE

N20688 001
DEC 18, 1996

ONDANSETRON

TABLET, ORALLY DISINTEGRATING; ORAL
ZOFRAN ODT

GLAXOSMITHKLINE EQ 4MG BASE

+ EQ 8MG BASE

N20781 001
JAN 27, 1999
N20781 002
JAN 27, 1999

OLSALAZINE SODIUM

CAPSULE; ORAL
DIPENTUM

+ PHARMACIA AND UPJOHN 250MG

N19715 001
JUL 31, 1990

ONDANSETRON HYDROCHLORIDE

INJECTABLE; INJECTION

ZOFRAN

+ GLAXOSMITHKLINE EQ 2MG BASE/ML

ZOFRAN IN PLASTIC CONTAINER

+ GLAXOSMITHKLINE EQ 0.64MG BASE/ML

ZOFRAN PRESERVATIVE FREE

+ GLAXOSMITHKLINE EQ 2MG BASE/ML

N20007 001
JAN 04, 1991
N20403 001
JAN 31, 1995
N20007 003
DEC 10, 1993

OMEPRAZOLE

CAPSULE, DELAYED REL PELLETS; ORAL

OMEPRAZOLE

AB ANDRX PHARMS 10MG

AB 20MG

N75347 001
NOV 16, 2001
N75347 002
NOV 16, 2001

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ATTACHMENT 2

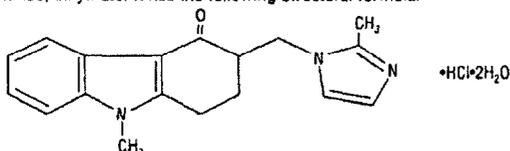
ZOFRAN® (ondansetron hydrochloride) Tablets

ZOFRAN ODT® (ondansetron) Orally Disintegrating Tablets

ZOFRAN® (ondansetron hydrochloride) Oral Solution

DESCRIPTION

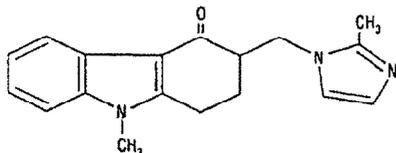
The active ingredient in ZOFRAN Tablets and ZOFRAN Oral Solution is ondansetron hydrochloride (HCl) as the dihydrate, the racemic form of ondansetron and a selective blocking agent of the serotonin 5-HT₃ receptor type. Chemically it is (±) 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one,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



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

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

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



The empirical formula is C₁₈H₁₉N₃O 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 24-mg ZOFRAN Tablet for oral administration contains ondansetron HCl dihydrate equivalent to 24 mg of ondansetron. Each tablet also contains the inactive ingredients lactose, microcrystalline cellulose, pregelatinized starch, hypromellose, magnesium stearate, titanium dioxide, triacetin, iron oxide yellow (8-mg tablet only), and iron oxide red (24-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,

ZOFRAN® (ondansetron hydrochloride) Tablets ZOFRAN ODT® (ondansetron) Orally Disintegrating Tablets ZOFRAN® (ondansetron hydrochloride) Oral Solution

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-HT₃ receptor antagonist. While its mechanism of action has not been fully characterized, ondansetron 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 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-HT₃ 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-HT₃ 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.

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

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 at concentrations likely to significantly contribute to the biological activity of ondansetron.

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

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

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

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.

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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 Tables 1 and 2 taken from 2 studies.

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

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

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

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

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

In patients with mild-to-moderate hepatic impairment, clearance is reduced 2-fold and mean half-life is increased to 11.6 hours compared to 5.7 hours in normals. In patients with severe hepatic impairment (Child-Pugh¹ score of 10 or greater), clearance is reduced 2-fold to 3-fold and apparent volume of distribution is increased with a resultant increase in half-life to 20 hours. In patients with severe hepatic impairment, a total daily dose of 8 mg should not be exceeded.

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

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.

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

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CLINICAL TRIALS

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

The first trial compared oral doses of ondansetron 24 mg once a day, 8 mg twice a day, and 32 mg once a day in 357 adult cancer patients receiving chemotherapy regimens containing cisplatin ≥50 mg/m². A total of 68% of patients in the ondansetron 24-mg once a day group, 55% in the ondansetron 8-mg twice a day group, and 55% in the ondansetron 32-mg once a day group completed the 24-hour study period with 0 emetic episodes and no rescue antiemetic medications, the primary endpoint of efficacy. Each of the 3 treatment groups was shown to be statistically significantly superior to a historical placebo control.

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

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

Moderately Emetogenic Chemotherapy: In 1 double-blind US study in 67 patients, ZOFTRAN Tablets 8 mg administered twice a day 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 in Table 3:

Table 3. Emetic Episodes: Treatment Response

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

* 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 ZOFTRAN 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 2 emetic episodes.

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

In 1 double-blind US study in 336 patients, ZOFTRAN Tablets 8 mg administered twice a day were as effective as ZOFTRAN Tablets 8 mg administered 3 times a day in preventing nausea and vomiting induced by cyclophosphamide-based chemotherapy containing either methotrexate or doxorubicin. Treatment response is based on the

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total number of emetic episodes over the 3-day study period. The results of this study are summarized in Table 4:

Table 4. Emetic Episodes: Treatment Response

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

* 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 ZOFTRAN 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 ZOFTRAN Tablet was administered 3 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 ZOFTRAN Tablets 8 mg 3 times daily 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 1 to 2 emetic episodes occurred in 43 (11%) of the re-treatment courses.

Pediatric Studies: Three open-label, uncontrolled, foreign trials have been performed with 182 pediatric 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 ZOFTRAN® (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 ZOFTRAN 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 ZOFTRAN Tablets 4 mg 3 times a day to be similar to those in patients 12 to 18 years of age who received ZOFTRAN Tablets 8 mg 3 times daily. Thus, prevention of emesis in these pediatric patients was essentially the same as for patients older than 18 years of age. Overall, ZOFTRAN Tablets were well tolerated in these pediatric patients.

Radiation-Induced Nausea and Vomiting: Total Body Irradiation: In a randomized, double-blind study in 20 patients, ZOFTRAN 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 1320 cGy. Patients received 3 fractions for 3 days, then 2 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 1000 cGy) over an anterior or posterior field size of ≥ 80 cm² to the abdomen. Patients received the first dose of ZOFTRAN Tablets (8 mg) or metoclopramide (10 mg) 1 to 2 hours before radiotherapy. If radiotherapy was given in the morning, 2 additional doses of study treatment were given (1 tablet late afternoon and 1 tablet before bed-

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time). If radiotherapy was given in the afternoon, patients took only 1 further tablet that day before bedtime. Patients continued the oral medication on a 3 times a day 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 cm² to the abdomen. Patients received the first dose of ZOFTRAN Tablets (8 mg) or prochlorperazine (10 mg) 1 to 2 hours before the patient received the first daily radiotherapy fraction, with 2 subsequent doses on a 3 times a day basis. Patients continued the oral medication on a 3 times a day 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 2 double-blind studies (1 US study, 1 foreign) involving 865 patients. ZOFTRAN 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 ZOFTRAN Tablets to ZOFTRAN Injection has been performed.

INDICATIONS AND USAGE

1. Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥ 50 mg/m².
2. Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.
3. Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen.
4. 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, ZOFTRAN Tablets, ZOFTRAN ODT Orally Disintegrating Tablets, and ZOFTRAN Oral Solution are recommended even where the incidence of postoperative nausea and/or vomiting is low.

CONTRAINDICATIONS

ZOFTRAN Tablets, ZOFTRAN ODT Orally Disintegrating Tablets, and ZOFTRAN 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-HT₃ 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 ZOFTRAN 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 ZOFTRAN 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

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ZOFRAN® (ondansetron hydrochloride) Oral Solution

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.

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

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/day, respectively. Ondansetron was not mutagenic in standard tests for mutagenicity. Oral administration of ondansetron up to 15 mg/kg/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/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 pediatric patients 4 years of age or younger (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION sections for use in pediatric patients 4 to 18 years of age).

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

ADVERSE REACTIONS

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

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

Table 5. Principal Adverse Events in US Trials: Single Day Therapy With 24-mg ZOFRAN Tablets (Highly Emetogenic Chemotherapy)

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

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The adverse events in Table 6 have been reported in ≥5% of adults receiving either 8 mg of ZOFRAN Tablets 2 or 3 times a day for 3 days or placebo in 4 trials. These patients were receiving concurrent moderately emetogenic chemotherapy, primarily cyclophosphamide-based regimens.

Table 6. Principal Adverse Events in US Trials: 3 Days of Therapy With 8 mg ZOFRAN Tablets (Moderately Emetogenic Chemotherapy)

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

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 adverse events in Table 7 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.

Table 7. Frequency of Adverse Events From Controlled Studies With ZOFRAN Tablets (Postoperative Nausea and Vomiting)

Adverse Event	Ondansetron 16 mg (n = 550)	Placebo (n = 531)
Wound problem	152 (28%)	162 (31%)
Drowsiness/sedation	112 (20%)	122 (23%)
Headache	49 (9%)	27 (5%)
Hypoxia	49 (9%)	35 (7%)
Pyrexia	45 (8%)	34 (6%)
Dizziness	36 (7%)	34 (6%)

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Gynecological disorder	36 (7%)	33 (6%)
Anxiety/agitation	33 (6%)	29 (5%)
Bradycardia	32 (6%)	30 (6%)
Shiver(s)	28 (5%)	30 (6%)
Urinary retention	28 (5%)	18 (3%)
Hypotension	27 (5%)	32 (6%)
Pruritus	27 (5%)	20 (4%)

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.

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

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

Hepatobiliary: Liver enzyme abnormalities

Lower Respiratory: Hiccups

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

Skin: Urticaria

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 150 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.

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

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 1 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 Highly Emetogenic Cancer Chemotherapy: The recommended adult oral dosage of ZOFRAN is a single 24-mg tablet administered 30 minutes before the start of single-day highly emetogenic chemotherapy, including cisplatin ≥ 50 mg/m². Multiday, single-dose administration of ZOFRAN 24-mg Tablets has not been studied.

Pediatric Use: There is no experience with the use of 24-mg ZOFRAN Tablets in pediatric patients.

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

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 pediatric patients 12 years of age and older, the dosage is the same as for adults. For pediatric 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 ZOFRAN Oral Solution given 3 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 3 times a day (every 8 hours) for 1 to 2 days after completion of chemotherapy.

Geriatric Use: 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 3 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 pediatric patients.

Geriatric Use: The dosage recommendation is the same as for the general population.
Postoperative Nausea and Vomiting: The recommended dosage is 16 mg given 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 pediatric patients.

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

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

Dosage Adjustment for Patients With Impaired Hepatic Function: In patients with severe hepatic impairment (Child-Pugh¹ score of 10 or greater), clearance is reduced and apparent volume of distribution is increased with a resultant increase in half-life. In such patients, a total daily dose of 8 mg should not be exceeded.

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ZOFRAN ODT® (ondansetron) Orally Disintegrating Tablets
ZOFRAN® (ondansetron hydrochloride) Oral Solution**

**ZOFRAN® (ondansetron hydrochloride) Tablets
ZOFRAN ODT® (ondansetron) Orally Disintegrating Tablets
ZOFRAN® (ondansetron hydrochloride) Oral Solution**

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).

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

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

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

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

ZOFRAN ODT Orally Disintegrating Tablets, 4 mg (as 4 mg ondansetron base) are white, round and plano-convex tablets debossed with a "24" on one 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 debossed with a "28" on one side in unit dose packs of 10 tablets (NDC 0173-0570-04) and 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.

REFERENCE

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



GlaxoSmithKline
Research Triangle Park, NC 27709

ZOFRAN Tablets and Oral Solution:
GlaxoSmithKline
Research Triangle Park, NC 27709

ZOFRAN ODT Orally Disintegrating Tablets:
Manufactured for GlaxoSmithKline
Research Triangle Park, NC 27709
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ATTACHMENT 3

Hydrochloride Tablet was superior to relevant historical placebo control in the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin 50 mg/m². Steroid administration was excluded from these clinical trials. More than 90% of patients receiving a cisplatin dose ≥50 mg/m² in the historical placebo comparator experienced vomiting in the absence of antiemetic therapy.

The first trial compared oral doses of ondansetron 24 mg once a day, 8 mg twice a day, and 32 mg once a day in 357 adult cancer patients receiving chemotherapy regimens containing cisplatin ≥50 mg/m². A total of 65% of patients in the ondansetron 24 mg once a day group, 55% in the ondansetron 8 mg twice a day group, and 55% in the ondansetron 32 mg once a day group completed the 24-hour study period with zero emetic episodes and no rescue antiemetic medications, the primary endpoint of efficacy. Each of the three treatment groups was shown to be statistically significantly superior to a historical placebo control.

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

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

Moderately Emetogenic Chemotherapy: In one double-blind US study in 67 patients, Ondansetron Hydrochloride Tablets 8 mg administered twice a day 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 in Table 3.

Table 3: Emetic Episodes: Treatment Response

	Ondansetron Hydrochloride Tablets* 8 mg b.i.d	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 Ondansetron Hydrochloride 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, Ondansetron Hydrochloride Tablets 8 mg administered twice a day were as effective as Ondansetron Hydrochloride 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 in Table 4.

Table 4: Emetic Episodes: Treatment Response

	Ondansetron	
	8-mg b.i.d Hydrochloride Ondansetron Tablets*	8-mg t.i.d Hydrochloride Ondansetron 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	49 (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 Ondansetron Hydrochloride 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 Ondansetron Hydrochloride 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 Ondansetron Hydrochloride 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 pediatric 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 Ondansetron Hydrochloride 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 Ondansetron Hydrochloride 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 Ondansetron Hydrochloride Tablets 4 mg three times a day to be similar to those in patients 12 to 18 years of age who received Ondansetron Hydrochloride Tablets 8 mg three times daily. Thus, prevention of emesis in these pediatric patients was essentially the same as for patients older than 18 years of age. Overall, Ondansetron Hydrochloride Tablets were well tolerated in these pediatric patients.

Radiation-Induced Nausea and Vomiting: Total Body Irradiation: In a randomized, double-blind study in 20 patients, Ondansetron Hydrochloride 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 (12.0 cGy per fraction) over 4 days for a total of 1320 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 1000 cGy) over an anterior or posterior field size of ≥80 cm² to the abdomen. Patients received the first dose of Ondansetron Hydrochloride 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 cm² to the abdomen. Patients received the first dose of Ondansetron Hydrochloride 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 saline or enteral) were evaluated in two double-blind studies (one US study, one foreign) involving 865 patients. Ondansetron Hydrochloride 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 Ondansetron Hydrochloride Tablets to Ondansetron Hydrochloride Injection has been performed.

INDICATIONS AND USAGE:

- Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥50 mg/m².
- Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.
- 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.
- 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, Ondansetron Orally Disintegrating Tablets are recommended even where the incidence of postoperative nausea and/or vomiting is low.

CONTRAINDICATIONS: Ondansetron Orally Disintegrating Tablets 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-HT₃ 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, Phenylethanamines:** Phenylethanamine patients should be informed that Orally Disintegrating Tablets contain phenylethylamine (a component of aspartame). Each 4 mg and 8 mg orally disintegrating tablet contains <0.03 mg phenylethylamine.

Patients should be instructed not to remove Ondansetron Orally Disintegrating 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 P388 mouse leukemia model is not affected by ondansetron. In humans, carbimazole, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.

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

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

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 pediatric patients 4 years of age or younger (see CLINICAL PHARMACOLOGY AND DOSAGE AND ADMINISTRATION sections for use in pediatric patients 4 to 18 years of age).

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

ADVERSE REACTIONS: The following have been reported as adverse events in clinical trials of patients treated with ondansetron, the active ingredient of Ondansetron Orally Disintegrating Tablets. A causal relationship to therapy with ondansetron has been unclear in many cases.

Chemotherapy-Induced Nausea and Vomiting: The adverse events in Table 5 have been reported in ≥5% of adult patients receiving a single 24 mg Ondansetron Hydrochloride Tablet in two trials. These patients were receiving concurrent highly emetogenic cisplatin-based chemotherapy regimens (cisplatin dose ≥50 mg/m²).

Table 5: Principal Adverse Events in US Trials: Single Day Therapy With 24 mg Ondansetron Hydrochloride Tablets (Highly Emetogenic Chemotherapy)

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

The following adverse events have been reported in ≥5% of adults receiving either 8 mg of Ondansetron Hydrochloride Tablets two or three times a day for 3 days or placebo in four trials. These patients were receiving concurrent moderately emetogenic chemotherapy, primarily cyclophosphamide-based regimens.

Table 6: Principal Adverse Events in US Trials: 3 Days of Therapy With 8 mg Ondansetron Hydrochloride Tablets (Moderately Emetogenic Chemotherapy)

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

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 Ondansetron Hydrochloride 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 Ondansetron Hydrochloride was unclear.

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

Postoperative Nausea and Vomiting: The adverse events in Table 7 have been reported in >5% of patients receiving Ondansetron Hydrochloride 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