

POLICY & PRACTICE

Stem Cell Ethics

All institutions conducting research using human embryonic stem cells should establish special oversight committees to review the research, according to a report that was issued by the National Research Council and the Institute of Medicine. But these committees should replace existing institutional review boards, the report stated. The report includes research guidelines, such as one stating that left-over blastocysts at in-vitro fertilization clinics should not be donated for research without consent and another advising re-

searchers not to ask fertility doctors to create more embryos than necessary for reproductive treatments. "A standard set of requirements for deriving, storing, distributing, and using embryonic stem cell lines—one to which the entire U.S. community adheres—is the best way for this research to move forward," said Richard O. Hynes, Ph.D., who is the cochair of the committee and professor of cancer research at the Massachusetts Institute of Technology. The report is available online at <http://national-academies.org>.

Obtaining Emergency Contraception

Emergency contraception may not be available at hospitals even in states that require emergency departments to provide it, according to a study published in the *Annals of Emergency Medicine*. The study, published online in May, is based on a telephone survey of 587 Catholic hospitals and 615 non-Catholic hospitals. About 42% of non-Catholic hospitals and 55% of Catholic hospitals reported that their emergency department does not dispense emergency contraception under any circumstance. About one-third of all hospitals surveyed said emergency contraception is available with some restrictions. For

example, some hospitals require a woman to take a pregnancy test first, and others will only provide it to victims of sexual assault. The survey was conducted by Ibis Reproductive Health, a Cambridge, Mass.-based women's reproductive-health research and advocacy group.

Improving the WIC Program

Changes are needed to the Special Supplemental Nutrition Program for Women, Infants, and Children to promote breastfeeding and encourage participants to eat more whole grains, fruits, and vegetables, according to the Institute of Medicine. In its report, the IOM recommends that WIC revise its food packages for women who are breastfeeding. The packages should include greater amounts and a wider variety of food such as milk, eggs, cheese, and whole grains. The IOM also recommended that participants be given vouchers or coupons for fresh produce totaling \$10 per month for each woman and \$8 per month for each child. In fiscal year 2003, an average of 7.63 million people received WIC benefits each month. About 3.82 million were children, 1.95 million were infants, and 1.86 million were women. The report is available online at <http://national-academies.org>.

Teen's Abortion Allowed

A Florida judge last month cleared the way for a 13-year-old girl to have an abortion. This comes as state lawmakers consider legislation to require parental notification when minors seek abortions. The case was controversial in Florida, where the girl is a ward of the state. She had initially sought help from her caseworker to seek an abortion, but the state's Department of Children and Families had obtained a court order to block the procedure. That order was overturned after the American Civil Liberties Union filed an appeal on the teen's behalf and Florida Gov. Jeb Bush (R) announced he would not block her efforts to obtain an abortion. The state's Supreme Court struck down a parental-notification law in 1999, but last year a ballot measure was passed to amend the constitution to allow the law to be enacted.

Lobbying for Breast-Feeding

Mothers descended on Capitol Hill last month to support legislation that would offer incentives for women to breast-feed or pump milk while at work. The Breast-Feeding Promotion Act of 2005 (H.R. 2122) would provide tax incentives to businesses that establish private lactation areas in the workplace and would amend the Civil Rights Act of 1964 to provide protections for breast-feeding mothers at work. The bill also seeks to make the purchase of breast-feeding equipment tax deductible. "We want to make sure that any woman who decides to breast-feed will get all the support she needs," said Rep. Carolyn Maloney (D-N.Y.), one of the sponsors of the legislation. "The United States has one of the lowest breast-feeding rates in the industrialized world and one of the highest rates of infant mortality; we need to reverse that." The bill had been previously introduced in the last two sessions of Congress.

—Mary Ellen Schneider

BRIEF SUMMARY

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

The following is a brief summary only; see full prescribing information for complete product information.

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 distention.

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 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 (see CLINICAL PHARMACOLOGY, Pharmacokinetics in full prescribing information). Because ondansetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes (CYP3A4, CYP2D6, CYP1A2), 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. **Phenyltoin, Carbamazepine, and Rifampicin:** In patients treated with potent inducers of CYP3A4 (i.e., phenytoin, carbamazepine, and rifampicin), the clearance of ondansetron was significantly increased and ondansetron blood concentrations were decreased. However, on the basis of available data, no dosage adjustment for ondansetron is recommended. Although no pharmacokinetic drug interaction between ondansetron and tramadol has been observed, data from 2 small studies indicate that ondansetron may be associated with an increase in patient controlled administration of tramadol. **Chemotherapy:** 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 of full prescribing information 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 section of full prescribing information).

ADVERSE REACTIONS

The following have been reported as adverse events in clinical trials of patients treated with ondansetron, the active ingredient of ZOFTRAN. A causal relationship to therapy with ZOFTRAN has been unclear in many cases. **Chemotherapy-Induced Nausea and Vomiting:** The adverse events in Table 1 have been reported in ≥5% of adult patients receiving a single 24-mg ZOFTRAN Tablet in 2 trials. These patients were receiving concurrent highly emetogenic cisplatin-based chemotherapy regimens (cisplatin dose ≥50 mg/m²).

Table 1. Principal Adverse Events in US Trials: Single Day Therapy With 24-mg ZOFTRAN 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%)

The adverse events in Table 2 have been reported in ≥5% of adults receiving either 8 mg of ZOFTRAN 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 2. Principal Adverse Events in US Trials: 3 Days of Therapy With 8-mg ZOFTRAN 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 ZOFTRAN 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 ZOFTRAN was unclear.

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

Postoperative Nausea and Vomiting: The adverse events in Table 3 have been reported in ≥5% of patients receiving ZOFTRAN 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 3. Frequency of Adverse Events From Controlled Studies With ZOFTRAN 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%)
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 ZOFTRAN 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 ZOFTRAN. 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 ZOFTRAN.

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 ZOFTRAN 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.

 GlaxoSmithKline

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ZOFTRAN ODT Orally Disintegrating Tablets:
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References: 1. Kovac AL. Prevention and treatment of postoperative nausea and vomiting. *Drugs*. 2000;59:213-243. 2. Marcus JR, Few JW, Chao JD, Fine NA, Mustoe TA. The prevention of emesis in plastic surgery: a randomized, prospective study. *Plast Reconstr Surg*. 2002;109:2487-2494. 3. Scuderi P, Pearman M, Kovac A, et al. Single-dose oral ondansetron prevents nausea and vomiting after inpatient surgery. *J Appl Res*. 2001;1:49-56. 4. Rust M, Cohen LA. Single oral dose ondansetron in the prevention of postoperative nausea and emesis. *Anaesthesia*. 1994;49(suppl):16-23. 5. Data on file, GlaxoSmithKline.