

## POLICY &amp; PRACTICE

## S. Dakota Faces Abortion Referendum

The question of whether South Dakota's recently passed abortion ban will stand is likely to be decided by the voters. A coalition called the South Dakota Campaign for Healthy Families submitted more than 38,000 signatures to refer the state abortion ban to the ballot in November, exceeding the 16,728 signatures required under state law. South Dakota Gov. Mike Rounds (R) signed the ban into law in March. The law was set to take effect on July 1, but if enough signatures were certified as valid, the law was to be suspended pending the

results of the November ballot referendum. If the ban takes effect it would make it a felony to perform an abortion except in cases where the mother's life is in danger. At press time, the South Dakota secretary of state's office was in the process of reviewing the signatures.

## Harvard Launches Stem Cell Project

Scientists at Harvard University and Children's Hospital Boston have been given the green light to begin research using somatic cell nuclear transfer in an effort to develop treatments for diabetes, blood disor-

ders, and neurodegenerative diseases. The research, which will involve human embryonic stem cells, will be privately funded since the federal government will not provide money for research using human embryonic stem cells derived after August 9, 2001. The efforts were praised by the Coalition for the Advancement of Medical Research, which advocates for federal funding of stem cell research. "In the absence of federal support for and oversight of this type of research, CAMR is pleased that institutions like Harvard have taken the necessary steps to ensure that therapeutic cloning research happens in a manner fully consistent with the ethics and scientific

standards in place for all research involving human subjects and tissues," CAMR President Sean Tipton said in a statement.

## Women and Medical Research

More than 60% of women age 50 years and older who have participated in a medical research study would "definitely" or "probably" do it again, according to a survey released by the Society for Women's Health Research. The group commissioned the national telephone survey of more than 1,000 women age 50 years and older. A similar survey was conducted in 2003. Overall, 10% of women age 50 years and older have participated in some type of medical research, the 2006 survey found, down slightly from 12% in 2003. However, a growing number of women said they aren't interested in or don't believe in medical research in the 2006 survey. Nearly 16% of women surveyed cited lack of interest as a reason for not wanting to participate, compared with about 9% in the 2003 survey.

## Postpartum Depression Targeted

A new bill, introduced in the U.S. Senate last month, aims to help find the cause and the cure for postpartum depression. The legislation would award grants to states to educate and screen new mothers for postpartum depression and support programs that assist women with postpartum depression. The Mom's Opportunity to Access Help, Education, Research, and Support for Postpartum Depression Act or the MOTHERS Act (S. 3529) was introduced by Sen. Richard Durbin (D-Ill.) and Sen. Robert Menendez (D-N.J.). The so-called "baby blues" affect up to 80% of new mothers, with postpartum depression affecting 10%-20% of new mothers and postpartum psychosis occurring in 1:1,000 new mothers, according to the bill. The legislation calls on the secretary of Health and Human Services to organize a series of national meetings to develop a research plan for postpartum depression and psychosis. The plan should include basic research into the cause of postpartum conditions, epidemiologic studies looking at the natural history of the disorder, the development of improved diagnostic techniques, and clinical research into new treatments such as biologic agents, according to the legislation. The bill was referred to the Senate Committee on Health, Education, Labor, and Pensions.

## FDA Infected by Politics, Most Think

A majority of Americans—82%—believe the Food and Drug Administration is greatly influenced by politics when making decisions about the safety and efficacy of new prescription drugs, according to a Wall Street Journal online Harris Interactive poll. The finding was similar across parties, with 87% of Democrats, 77% of Republicans, and 88% of Independents saying they thought that politics outweighed science greatly or to some extent in decision-making. The survey of more than 2,300 adults was conducted in mid-May. In addition, almost 60% said the agency is doing a fair or poor job in ensuring the safety and efficacy of new drugs. Only 36% said the FDA was doing an excellent or good job. That is a reversal from 2 years ago, when 56% had a positive view, and 37% a negative view, of the FDA.

—Mary Ellen Schneider

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-HT<sub>2</sub> receptor antagonists.

## PRECAUTIONS

**General:** 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. Rarely and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been reported.

**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. **Phenytoin, 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 for patients on these drugs. **Tramadol:** 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/m<sup>2</sup>).

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.

## BRIEF SUMMARY

**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.

**Cardiovascular:** Rarely and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been reported.

**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

**Special Senses: Eye Disorders:** Cases of transient blindness, predominantly during intravenous administration, have been reported. These cases of transient blindness were reported to resolve within a few minutes up to 48 hours.

## 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.



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ZOFTRAN Tablets and Oral Solution:  
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ZOFTRAN ODT Orally Disintegrating Tablets:  
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February 2006 RL-2237

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Z03482R0

December 2005

**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.