

## POLICY &amp; PRACTICE

## Salary Affects Specialty Choice

When it comes to choosing a specialty, U.S. medical graduates are more concerned with their earning power than with medical liability costs, according to a study published in the September issue of *Obstetrics and Gynecology*. Procedure-based and hospital-based specialties, which generally are associated with higher incomes, are the most likely to have residency positions filled by U.S. medical graduates, the researchers found, even when the specialty had higher professional liability costs. For example, U.S. medical students filled

more than 90% of the residency positions in neurosurgery and orthopedic surgery where medical liability insurance costs are high but so are average incomes. In contrast, U.S. students filled 70% of the available residency positions in obstetrics and gynecology, according to the American College of Obstetricians and Gynecologists. But the researchers noted that students also may be attracted to high-earning fields because of the technical challenges or the ability to have a more controllable lifestyle. The results are based on data from the 2004 National Resident

Matching Program, the American Medical Association, the Medical Group Management Association, and a major Massachusetts liability insurer.

## Greater Folic Acid Fortification

Officials at the March of Dimes are calling on the federal government to require higher levels of folic acid fortification in grain food. The request, which reflects a long-held policy of the March of Dimes, comes on the heels of new research showing that folic acid fortification in grain foods has resulted in a one-third drop in serious birth defects of the brain and spine. The Food and Drug Administration cur-

rently requires 140 mcg of folic acid per 100 g of grain. Since 1996, the March of Dimes has recommended that the FDA set the level in enriched grain foods at 350 mcg per 100 g of grain.

## Pesticide Studies

A proposal from the Environmental Protection Agency would ban the inclusion of pregnant women and children in all new third-party intentional dosing research involving pesticides intended for submission to the agency. The proposal says that EPA officials will neither conduct nor support any intentional dosing studies that involve pregnant women or children. "We are pursuing a rigorous set of protections for human research participants," Susan B. Hazen, principal deputy assistant administrator in the EPA's Office of Prevention, Pesticides, and Toxic Substances said in a statement. The agency has come under fire recently from congressional Democrats for relying on studies that involve intentionally dosing human subjects with pesticides. More information is available at [www.epa.gov/oppfead1/guidance/human-test.htm](http://www.epa.gov/oppfead1/guidance/human-test.htm).

## Reporting Neonatal Herpes

A group of experts in obstetrics and gynecology and pediatrics is calling on the Centers for Disease Control and Prevention to request reporting of cases of neonatal herpes from all states and U.S. territories. The call to action, which was published in the September issue of the journal *Sexually Transmitted Diseases*, notes that a lack of reliable epidemiological data may be partly responsible for the continued development of neonatal herpes cases. While diseases such as congenital syphilis are reportable in 47 states, only 7 states—Connecticut, Florida, Massachusetts, Nebraska, Ohio, South Dakota, and Washington—require reporting of neonatal herpes. The CDC can request reports on various conditions, but the states have the regulatory authority to require reporting. The epidemiological data from reported cases of neonatal herpes would help to resolve debates over testing, treatment, and prevention strategies, the researchers wrote. The analysis was supported by GlaxoSmithKline Inc.

## Census Bureau Statistics

The Census Bureau reports that 45.8 million Americans were without health insurance in 2004, up from 45 million in 2003. While the increase is statistically small, it means that "an additional 860,000 Americans live without the safety net of health insurance," J. Edward Hill, M.D., president of the American Medical Association, said in a statement. "As the decrease in employment-based health insurance continues, the AMA renews its call for health insurance solutions that put patients in the driver's seat, along with their physicians," Dr. Hill said. Some of these solutions may include refundable tax credits inversely related to income and individually selected and owned health insurance, he said. In other statistics, the number of people with health insurance increased by 2 million to 245.3 million between 2003 and 2004. Those covered by government health insurance rose from 76.8 million in 2003 to 79 million.

—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-HT<sub>2</sub> 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 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 16 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 U.S. and foreign-controlled clinical trials, for which there were subgroup analyses, 338 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.

**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.

gsk GlaxoSmithKline

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