

FDA to Sharpen Postmarketing Drug Safety Focus

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The Food and Drug Administration said it will beef up oversight of prescription drug safety, with a focus on risks and benefits once a product has been launched into the marketplace.

The initiatives were announced in January in a long-awaited response to September's Institute of Medicine critique of the agency's pharmaceutical safety monitoring.

The FDA said it had taken a close look at the IOM's 25 recommendations, and that it would focus its efforts on three major areas:

1. Strengthening the science used during product reviews and finding new tools to detect safety issues from preclinical testing through postmarketing.
2. Improving communications, especially about risk, to patients, physicians, and other interested parties.
3. Improving management practices.

The IOM criticized an agency culture that it saw as too concentrated on drug approval at the expense of product safety.

Some of the FDA initiatives are underway. Others were published in the Federal Register as part of recommendations for the reauthorization of the Prescription Drug User Fee Act. Under the next PDUFA law, which if enacted would begin in fiscal 2008, the FDA aims to collect \$29 million from drug makers over 5 years specifically for postmarketing safety programs.

Key among the initiatives announced in late January is a "report card" on the post-marketing safety of new molecular entities. FDA has proposed a pilot feasibility study this year. These regularly scheduled reports would encompass data from the Adverse Events Reporting System, epidemiologic studies, postmarketing clinical trials, and "mining" of various other databases. The first report would come 18 months after a drug's launch. The goal of this effort is "to identify potential safety concerns early in the product life cycle," according to the FDA.

The FDA also proposed sharing data more often with other agencies, and said it was already collaborating with the Agency for Health Care Quality and Research, the Centers for Disease Control and Prevention, and the Veterans Affairs department. The VA will provide real-world data on how its patients use pharmaceuticals and medical devices.

To address criticism that the FDA has not done a good job of communicating what it knows about a drug's risks on a timely basis, the agency said it could—and would—move quickly to establish a new advisory committee.

The FDA also said it would hold a public meeting in early March to explore the creation of a nationwide public-private medical product safety network. The agency envisions a network that would let both health care providers and regulators rapidly collect and exchange information about adverse events—and would do so at the point of care to help providers make better-informed treatment decisions.

American Medical Association board member Dr. Edward Langston said the AMA generally supported FDA's proposals. "The AMA agrees that the approaches used to communicate information to patients about the risks associated with drug products need significant improvement," Dr. Langston said in a statement.

Long-time FDA critics in Congress, however, said the agency had not gone far enough.

"Today's report is thoughtful, and provides important recommendations for administrative action, but only legislation can give FDA the tools it needs to ensure that the agency is the gold standard for safety," said Sen. Edward M. Kennedy (D-Mass.), who, along with Sen. Michael Enzi (R-Wyo.) soon will introduce a bill to further overhaul FDA's postmarketing safety program.

Sen. Christopher J. Dodd (D-Conn.) said that he and Sen. Chuck Grassley (R-Iowa) were also introducing a bill that would "re-vamp and prioritize the postmarket surveillance process within the Food and Drug Administration."

That bill, called the Food and Drug Administration Safety Act, would establish a Center for Postmarket Evaluation and Research for Drugs and Biologics. The Center would report directly to the FDA commissioner.

"Congress will act on FDA-related legislation this year, and meaningful structural reforms to the agency need to be a part of what Congress does with regard to drug safety," Sen. Grassley said. ■

Zegerid®

omeprazole/sodium bicarbonate

Brief Summary of Prescribing Information

INDICATIONS AND USAGE

Duodenal Ulcer

ZEGERID is indicated for short-term treatment of active duodenal ulcer. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy.

Gastric Ulcer

ZEGERID is indicated for short-term treatment (4-8 weeks) of active benign gastric ulcer. (See CLINICAL PHARMACOLOGY, Clinical Studies, Gastric Ulcer.)

Treatment of Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD

ZEGERID is indicated for the treatment of heartburn and other symptoms associated with GERD.

Erosive Esophagitis

ZEGERID is indicated for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy. (See CLINICAL PHARMACOLOGY, Clinical Studies.)

The efficacy of ZEGERID used for longer than 8 weeks in these patients has not been established. In the rare instance of a patient not responding to 8 weeks of treatment, it may be helpful to give up to an additional 4 weeks of treatment. If there is recurrence of erosive esophagitis or GERD symptoms (eg, heartburn), additional 4-8 week courses of omeprazole may be considered.

Maintenance of Healing of Erosive Esophagitis

ZEGERID is indicated to maintain healing of erosive esophagitis. Controlled studies do not extend beyond 12 months.

Reduction of Risk of Upper Gastrointestinal Bleeding in Critically Ill Patients

ZEGERID Powder for Oral Suspension 40 mg/1680 mg is indicated for the reduction of risk of upper GI bleeding in critically ill patients.

CONTRAINDICATIONS

ZEGERID is contraindicated in patients with known hypersensitivity to any components of the formulation.

PRECAUTIONS

General

Symptomatic response to therapy with omeprazole does not preclude the presence of gastric malignancy.

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole.

Each ZEGERID Capsule contains 1100 mg (13 mEq) of sodium bicarbonate (equivalent to 300 mg of Na+). Each packet of ZEGERID Powder for Oral Suspension contains 1680 mg (20 mEq) of sodium bicarbonate (equivalent to 460 mg of Na+).

The sodium content of ZEGERID products should be taken into consideration when administering to patients on a sodium restricted diet. Sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcaemia. Sodium bicarbonate should be used with caution in patients with Bartter's syndrome, hypokalaemia, respiratory alkalosis, and problems with acid-base balance. Long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome.

Information for Patients

ZEGERID should be taken on an empty stomach at least one hour prior to a meal.

ZEGERID is available either as 40 mg or 20 mg capsules with 1100 mg sodium bicarbonate. ZEGERID is also available either as 40 mg or 20 mg single-dose packets of powder for oral suspension with 1680 mg sodium bicarbonate.

Directions for Use: Capsules: Swallow intact capsule with food. DO NOT USE OTHER LIQUIDS. DO NOT OPEN CAPSULE AND SPRINKLE CONTENTS INTO FOOD.

Powder for Oral Suspension: Empty packet contents into a small cup containing 1-2 tablespoons of water. DO NOT USE OTHER LIQUIDS OR FOODS. Stir well and drink immediately. Refill cup with water and drink.

Drug Interactions

Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including omeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with INR and prothrombin time and warfarin may need to be monitored for increases in INR and prothrombin time. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P-450 system (eg, cyclosporine, disulfiram, benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with ZEGERID.

Because of its profound and long-lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (eg, ketoconazole, ampicillin esters, and iron salts). In the clinical efficacy trials, antacids were used concomitantly with the administration of omeprazole. Concomitant administration of omeprazole and alendronate has been reported to reduce the plasma levels of alendronate. Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Co-administration of omeprazole and clarithromycin have resulted in increases of plasma levels of omeprazole, clarithromycin, and 14-hydroxy-clarithromycin (see also CLINICAL PHARMACOLOGY, Pharmacokinetics).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (approximately 0.5 to 28.5 times the human dose of 40 mg/day, based on body surface area) produced gastric ECL cell carcinomas in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinomas seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (approximately 2.8 times the human dose of 40 mg/day, based on body surface area) for one year then followed for an additional year without the drug. No carcinomas were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. In a 52-week toxicity study in Sprague-Dawley rats, brain astrocytomas were found in a small number of males that received omeprazole at dose levels of 0.4, 2, and 16 mg/kg/day (about 0.1 to 3.3 times the human dose of 40 mg/day, based on body surface area). No astrocytomas were observed in female rats in this study. In a 2-year carcinogenicity study in Sprague-Dawley rats, no astrocytomas were found in males and females at the high dose of 140.8 mg/kg/day (about 28.5 times the human dose of 40 mg/day, based on body surface area). A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. A 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive. Omeprazole was positive for clastogenic effects in an *in vitro* human lymphocyte chromosomal aberration assay, in one of two *in vivo* mouse micronucleus tests, and in an *in vivo* bone marrow cell chromosomal aberration assay. Omeprazole was negative in the *in vitro* Ames Test, an *in vitro* mouse lymphoma cell forward mutation assay and an *in vivo* rat liver DNA damage assay.

Omeprazole at oral doses up to 138 mg/kg/day (about 28 times the human dose of 40 mg/day, based on body surface area) was found to have no effect on the fertility and general reproductive performance in rats.

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies on the use of omeprazole in pregnant women. The vast majority of reported experience with omeprazole during human pregnancy is first trimester exposure and the duration of use is rarely specified, e.g., intermittent vs. chronic. An expert review of published data on experiences with omeprazole use during pregnancy by TERIS—the Teratogen Information System—concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as fair).

Three epidemiologic studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy to the frequency of abnormalities among infants of women exposed to H2-receptor antagonists or other controls. A population-based prospective cohort epidemiologic study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy. In utero exposure to omeprazole was not associated with increased risk of any malformation (odds ratio 0.82, 95% CI 0.50-1.34), low birth weight or low Apgar score. The number of infants born with

ventricular septal defects and the number of stillborn infants was slightly higher in the omeprazole exposed infants than the expected number in the normal population. The author concluded that both effects may be random.

A retrospective cohort study reported on 689 pregnant women exposed to either H2-blockers or omeprazole in the first trimester (134 exposed to omeprazole). The overall malformation rate was 4.4% (95% CI 3.6-5.3) and the malformation rate for first trimester exposure to omeprazole was 3.6% (95% CI 1.5-8.1). The relative risk of malformations associated with first trimester exposure to omeprazole compared with nonexposed women was 0.9 (95% CI 0.3-2.2). The study could effectively rule out a relative risk greater than 2.5 for all malformations. Rates of preterm delivery or growth retardation did not differ between the groups.

A controlled prospective observational study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposures). The reported rates of major congenital malformations were 4% for the omeprazole group, 2% for controls exposed to nonteratogens, and 2.8% in disease-paired controls (background incidence of major malformations 1-5%). Rates of spontaneous and elective abortions, preterm deliveries, gestational age at delivery, and mean birth weight did not differ between the groups. The sample size in this study has 80% power to detect a 5-fold increase in the rate of major malformation.

Several studies have reported no apparent adverse short term effects on the infant when single dose oral or intravenous omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia.

Toxicology studies conducted in pregnant rats at doses up to 138 mg/kg/day (about 28 times the human dose of 40 mg/day, based on body surface area) and in pregnant rabbits at doses up to 69 mg/kg/day (about 28 times the human dose of 40 mg/day, based on body surface area) did not disclose any evidence for a teratogenic potential of omeprazole.

In rabbits, omeprazole in a dose range of 6.9 to 69 mg/kg/day (about 2.8 to 28 times the human dose of 40 mg/day, based on body surface area) produced dose-related increases in embryolethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138.0 mg/kg/day (about 2.8 to 28 times the human dose of 40 mg/day, based on body surface area).

Chronic use of sodium bicarbonate may lead to systemic alkalosis and increased sodium intake can produce edema and weight increase. There are no adequate and well-controlled studies in pregnant women. Because animal studies and studies in humans cannot rule out the possibility of harm, omeprazole should be used during pregnancy only if the potential benefit to pregnant women justifies the potential risk to the fetus.

Nursing Mothers

Omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. The concentration would correspond to 0.004 mg of omeprazole in 200 mL of milk. Because omeprazole is excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be taken to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. In addition, sodium bicarbonate should be used with caution in nursing mothers.

Pediatric Use

Clinical studies have been conducted evaluating delayed-release omeprazole in pediatric patients. There are no adequate and well-controlled studies in pediatric patients with ZEGERID.

Geriatric Use

Omeprazole was administered to over 2000 elderly individuals (≥ 65 years of age) in clinical trials in the U.S. and Europe. There were no differences in safety and effectiveness between the elderly and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic studies with buffered omeprazole have shown the elimination rate was somewhat decreased in the elderly and bioavailability was increased. The plasma clearance of omeprazole was 250 mL/min (about half that of young subjects). The plasma half-life averaged one hour, about the same as that in nonelderly, healthy subjects taking ZEGERID. However, no dosage adjustment is necessary in the elderly. (See CLINICAL PHARMACOLOGY.)

ADVERSE REACTIONS

Omeprazole was generally well tolerated during domestic and international clinical trials in 3096 patients.

In the U.S. clinical trial population of 465 patients, the adverse experiences summarized in Table 11 were reported to occur in 1% or more of patients on therapy with omeprazole. Numbers in parentheses indicate percentages of the adverse experiences considered by investigators as possibly, probably or definitely related to the drug.

Table 11: Adverse Experiences Occurring in 1% or More of Patients on Omeprazole Therapy

	Omeprazole (n = 465)	Placebo (n = 64)	Ranitidine (n = 195)
Headache	6.9 (2.4)	6.3	7.7 (2.6)
Diarrhea	2.4 (0.4)	3.1 (1.6)	2.1 (0.5)
Abdominal Pain	2.4 (0.4)	3.1	2.1
Nausea	2.2 (0.9)	3.1	4.1 (0.5)
URI	1.9	1.6	2.6
Dizziness	1.5 (0.6)	0.0	2.6 (1.0)
Vomiting	1.5 (0.4)	4.7	1.5 (0.5)
Rash	1.5 (1.1)	0.0	0.0
Constipation	1.1 (0.9)	0.0	0.0
Cough	1.1	0.0	1.5
Asthenia	1.1 (0.2)	1.6 (1.6)	1.5 (1.0)
Back Pain	1.1	0.0	0.5

Table 12 summarizes the adverse reactions that occurred in 1% or more of omeprazole-treated patients from international double-blind, and open-label clinical trials in which 2,631 patients and subjects received omeprazole.

Table 12: Incidence of Adverse Experiences ≥ 1% Causal Relationship Not Assessed

	Omeprazole (n = 2631)	Placebo (n = 120)
Body as a Whole, site unspecified		
Abdominal pain	5.2	3.3
Asthenia	1.3	0.8
Digestive System		
Constipation	1.5	0.8
Diarrhea	3.7	2.5
Flatulence	2.7	5.8
Nausea	4.0	6.7
Vomiting	3.2	10.0
Acid regurgitation	1.9	3.3
Nervous System/Psychiatric		
Headache	2.9	2.5

A controlled clinical trial conducted in 359 critically ill patients, comparing ZEGERID 40 mg/1680 mg suspension once daily to i.v. cimetidine 1200 mg/day for up to 14 days. The incidence and total number of AEs experienced by ≥ 3% of patients in either group are presented in Table 13 by body system and preferred term.

Table 13: Number (%) of Critically Ill Patients with Frequently Occurring (≥ 3%) Adverse Events by Body System and Preferred Term

	ZEGERID® (N=178)	Cimetidine (N=181)
MedDRA Body System Preferred Term	All AEs n (%)	All AEs n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anaemia NOS	14 (7.9)	14 (7.7)
Anaemia NOS Aggravated	4 (2.2)	7 (3.9)
Thrombocytopenia	18 (10.1)	11 (6.1)
CARDIAC DISORDERS		
Atrial Fibrillation	11 (6.2)	7 (3.9)
Bradycardia NOS	7 (3.9)	5 (2.8)
Supraventricular Tachycardia	6 (3.4)	2 (1.1)
Tachycardia NOS	6 (3.4)	6 (3.3)
Ventricular Tachycardia	8 (4.5)	6 (3.3)
GASTROINTESTINAL DISORDERS*		
Constipation	8 (4.5)	8 (4.4)
Diarrhoea NOS	7 (3.9)	15 (8.3)

Gastric Hypomotility 3 (1.7) 6 (3.3)

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS

Hyperpyrexia 8 (4.5) 3 (1.7)

Oedema NOS 5 (2.8) 11 (6.1)

Pyrexia 36 (20.2) 29 (16.0)

INFECTIONS AND INFESTATIONS

Candidal Infection NOS 3 (1.7) 7 (3.9)

Oral Candidiasis 7 (3.9) 1 (0.6)

Sepsis NOS 9 (5.1) 9 (5.0)

Urinary Tract Infection NOS 4 (2.2) 6 (3.3)

INVESTIGATIONS

Liver Function Tests NOS Abnormal 3 (1.7) 6 (3.3)

METABOLISM AND NUTRITION DISORDERS

Fluid Overload 9 (5.1) 14 (7.7)

Hyperglycaemia NOS 19 (10.7) 21 (11.6)

Hyperkalaemia 4 (2.2) 6 (3.3)

Hypernatraemia 3 (1.7) 9 (5.0)

Hypocalcaemia 11 (6.2) 10 (5.5)

Hypokalaemia 6 (3.4) 8 (4.4)

Hypomagnesaemia 18 (10.1) 18 (9.9)

Hyponatremia 7 (3.9) 5 (2.8)

Hypophosphataemia 11 (6.2) 7 (3.9)

PSYCHIATRIC DISORDERS

Agitation 6 (3.4) 16 (8.8)

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS

Acute Respiratory Distress Syndrome 6 (3.4) 7 (3.9)

Nosocomial Pneumonia 20 (11.2) 17 (9.4)

Pneumothorax NOS 1 (0.6) 8 (4.4)

Respiratory Failure 3 (1.7) 6 (3.3)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS

Decubitus Ulcer 6 (3.4) 5 (2.8)

Rash NOS 10 (5.6) 11 (6.1)

VASCULAR DISORDERS

Hypertension NOS 14 (7.9) 6 (3.3)

Hypotension NOS 17 (9.6) 12 (6.6)

*Clinically significant UOI bleeding was considered an SAE but it is not included in this table.

Additional adverse experiences occurring in < 1% of patients or subjects in domestic and international trials conducted with omeprazole, or occurring since the drug was marketed, are shown below within each body system. In many instances, the relationship to omeprazole was unclear.

Body As a Whole

Allergic reactions, including, rarely, anaphylaxis (see also Skin below), fever, pain, fatigue, malaise, abdominal swelling.

Cardiovascular

Chest pain or angina, tachycardia, bradycardia, palpitation, elevated blood pressure, and peripheral edema.

Gastrointestinal

Pancreatitis (some fatal), anorexia, irritable colon, flatulence, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, dry mouth, stomatitis. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued.

Gastrointestinal carcinoids have been reported in patients with Zollinger-Ellison syndrome on long-term treatment with omeprazole. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors.

Hepatic

Mild and, rarely, marked elevations of liver function tests [ALT (SGPT), AST (SGOT), γ-glutamyl transpeptidase, alkaline phosphatase, and bilirubin (jaundice)]. In rare instances, overt liver disease has occurred, including hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy.

Metabolic/Nutritional

Hyponatremia, hypoglycemia, and weight gain.

Musculoskeletal

Muscle cramps, myalgia, muscle weakness, joint pain, and leg pain.

Nervous System/Psychiatric