

## NEWS FROM THE FDA

### Draft Guidance Given on Disclosures

The Food and Drug Administration has released draft guidance designed to provide more information on conflicts of interest involving members of its advisory committees and the waivers that allow them to participate in specific meetings.

The draft guidance is designed to bring agency policy in line with standard conflict of interest practice in the academic community, where medical journals re-

quire disclosures to be specific and thorough, the FDA said in a press briefing.

The FDA has 49 advisory committees with a total of more than 600 positions. Federal law allows the FDA to grant waivers so that experts who have conflicts of interest can participate in advisory committee meetings.

When a waiver is granted, federal law requires the FDA to disclose the type, nature, and magnitude of the conflict on its Web site. The law limits the number of

waivers to about 13% of all meeting participants, and in practice the agency grants waivers to fewer than 5%.

Under the draft guidance, the agency would expand the information disclosed about waivers so that the nature of the waiver granted and name of the company or institution involved also would be posted online prior to committee meetings.

Public comment will be accepted through June 20.

### Infusion Pumps to Be Regulated

The FDA will regulate the design and manufacture of infusion pumps in the wake of thousands of adverse event reports, the agency announced.

Over the past 5 years the FDA has received more than 56,000 reports of adverse events, including more than 500 deaths, related to the pumps.

During that period there have been 87 recalls of infusion pumps undertaken to address identified safety concerns. The problems have ranged from manufacturing defects to software bugs to user error.

The FDA is taking several steps to address the devices' problems at the level of manufacture.

In the interim, the agency is advising clinicians to use several strategies to reduce risk when using infusion pumps: Have a plan in place to respond to pump failures; prevent errors by labeling infusion pump channels and tubing; check settings of infusion pumps; check patients for signs of under- or overinfusion; and promptly report adverse events to the FDA.

The FDA has also ordered Baxter, the manufacturer of Colleague Volumetric Infusion pumps, to recall and destroy all of these pumps currently in use in the United States, because of a "longstanding failure to correct many serious problems" with the pumps.

The FDA said that hospitals and other users of these Colleague pumps will be receiving more information from Baxter and the FDA about making the transition to other infusion devices.

### GnRH Agonists Get Safety Study

The FDA is investigating whether treatment with a gonadotropin-releasing hormone agonist increases the risk of diabetes and cardiovascular events in men with prostate cancer.

In a statement issued May 3, the agency said that a preliminary analysis of several studies has identified an association between the use of gonadotropin-releasing hormone (GnRH) agonists and a "small increased risk" for diabetes, MI, stroke, and sudden death. The FDA has not made any conclusions about whether diabetes or these cardiovascular diseases are caused by treatment with these drugs, which are available in generic formulations and as brand-name products (Lupron, Eligard, Synarel, Trelstar, Vantas, Viadur, and Zoladex).

The studies under review are published observational studies and one randomized controlled clinical trial that compared androgen deprivation therapy using a GnRH agonist with other treatments in men with prostate cancer.

At this time, the FDA is advising that health care professionals should be aware of these potential risks "and carefully weigh the benefits and risks of GnRH agonists when determining a treatment for patients with prostate cancer," and that they should monitor patients for diabetes and cardiovascular disease when treated with one of these drugs.

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## Patients on PPI therapy aren't always "fire" proof

More than **46%** may still suffer from breakthrough heartburn.<sup>1-5</sup>

### What is their best escape route?

*Today's proton pump inhibitors may provide an answer for patients suffering from chronic heartburn. But, symptom elimination is less common than you may think.*

In a medical survey of 400 PPI users, more than 46% reported suffering from breakthrough heartburn.<sup>1</sup> Also, in a 2008 Gallup survey, 56% of people taking a prescription medication for their heartburn experienced breakthrough acid reflux.<sup>5</sup> And, breakthrough heartburn can have a substantial impact on everyday work activity.<sup>4</sup>

Although many try to manage by turning to over-the-counter remedies,<sup>1-4</sup> most never tell their doctor that they are using OTCs for their breakthrough episodes.<sup>1,2</sup>

#### More isn't always better when it comes to PPI therapy.

A common management option is to increase the PPI dose to twice daily.<sup>6</sup> However there are important reasons why this may not be the answer.

More than once-a-day PPI dosing, or long-term therapy, has been shown in a number of large studies to be associated with an increased risk of fractures,<sup>7-9</sup> (especially in patients over 50).<sup>7</sup> As well, PPIs have been associated with increases in certain types of infections.<sup>10-13</sup>

#### Is there an appropriate "partner" for PPI therapy?

PPI patients who are in the throes of breakthrough heartburn want fast relief. A possible answer is to partner their therapy with a fast-acting adjunct that compliments rather than conflicts with their PPI. Consider recommending a strong, trusted antacid that can provide the fast relief PPI patients need for heartburn breakthroughs.

#### TUMS Ultra. Goes to work in seconds to provide PPI patients with a fast escape route.

TUMS Ultra is the strongest TUMS we have ever made. With 1000mg of calcium carbonate per tablet, nothing works faster than TUMS Ultra. Also, there are no known drug interactions with PPI therapy. TUMS Ultra is conveniently portable, affordable, and pleasant tasting.

**Ask your PPI patients specifically about breakthrough heartburn, and consider recommending TUMS Ultra as their fast escape route.**



An ideal PPI partner



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<sup>1</sup> Jacobson BC, et al. Who is using chronic acid suppression therapy and why? *Am J Gastroenterol* 2003;98:151-58. <sup>2</sup> Jones R, et al. Does the treatment of gastroesophageal reflux disease (GERD) meet patients' needs? A survey based study. *Cur Med Res & Opinions* 2006;22:4:657-662. <sup>3</sup> Jacobson BC, Ferris TG, Shea T, et al. Who is using chronic acid suppression therapy and why? *Am J Gastroenterol* 2003;98:51-58. <sup>4</sup> Fass R, Sifrim D. Management of heartburn not responding to proton pump inhibitors. *GUT* 2009;58:295-309. <sup>5</sup> The 2008 Gallup Study of Acid Reflux / GERD Sufferers. Multi-sponsor Surveys Inc. March 2008 Detailed findings volume. <sup>6</sup> Chey WD, et al. Primary-Care Physicians' Perceptions and Practices on the Management of GERD: Results of a National Survey. *Am J Gastroenterol* 2005;100:1237-1242. <sup>7</sup> Yang YX, Lewis JD, et al. Long-term Proton Pump Inhibitor Therapy and Risk of Hip Fracture. *J Am Med Assoc* 2006;296:24:2947-2953. <sup>8</sup> Targownik LE, et al. Use of proton pump inhibitors and the risk of osteoporosis related fractures. *Clin Med Assoc J* Aug 12 2008;179(4):319-326. <sup>9</sup> Roux C, Briot K, et al. Increase in vertebral fracture risk in postmenopausal women using Omeprazole. *Calcif Tissue Int* 2009;84:13-19. <sup>10</sup> Lahajri R, et al. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004;292:1955-1960. <sup>11</sup> Ganani RB, et al. Therapy with Gastric Acidity Inhibitors Increases the Risk of Acute Gastroenteritis and Community-Acquired Pneumonia in Children. *Pediatrics* 2006;117(15):e817-e820. <sup>12</sup> Dial S, et al. Use of Gastric Acid-Suppressive Agents and the Risk of Community-Acquired Clostridium difficile-associated disease. *JAMA* 2005;294:23:2989-2995. <sup>13</sup> Dial S, Delaney JAC, Schneider V, Sausa S. Proton pump inhibitor use and risk of community-acquired Clostridium difficile-associated disease defined by prescription for oral vancomycin therapy. *CMAJ* 2006;175(7):745-748.



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These drugs are also used in women (for endometriosis-related pain, anemia associated with uterine fibroids before a hysterectomy, and palliative treatment for advanced breast cancer), but “there are no known studies that have evaluated the risk of diabetes and heart disease” in women taking these drugs, according to the FDA.

### Cancer Linked With Parkinson's Rx

An excess number of prostate cancer cases among men treated with the Parkinson's disease product that contains entacapone, carbidopa, and levodopa in a controlled clinical trial has prompted an FDA review of the combination drug's safety.

The agency is evaluating data from the Stalevo Reduction in Dyskinesia Evaluation–Parkinson's Disease (STRIDE-PD) study, which found that over a mean of almost 3 years, the number of prostate cancers diagnosed among the men treated with entacapone, carbidopa, and levodopa (marketed as Stalevo) was about four times higher than the cases diagnosed among those treated with the carbidopa and levodopa combination product (marketed as Sinemet). The FDA has not concluded that Stalevo increases the risk of prostate cancer.

“Healthcare professionals should be aware of this possible risk and follow current guidelines for prostate cancer screening” in patients on this combination product, and patients should not stop taking their medication unless directed to do so, the statement added.

### Warning Added to Thyroid Drug Label

Severe liver injuries have been associated with use of the antithyroid drug propylthiouracil, and the FDA has added a boxed warning to the product's label conveying this risk, the agency announced.

The warning for propylthiouracil (PTU) says that there have been reports of severe liver injury and acute liver failure, including fatalities, in those treated with the drug. Additionally, the agency said, for patients who are beginning treatment for hyperthyroidism, “it may be appropriate to reserve use of propylthiouracil for those who cannot tolerate other treatments such as methimazole, radioactive iodine, or surgery.”

PTU was approved in 1947 for the treatment of hyperthyroidism.

The warning also notes that because birth defects have been associated with use of the antithyroid drug methimazole during the first trimester, “propylthiouracil may be the treatment of choice during and just before the first trimester of pregnancy.”

The FDA issued a warning to health care professionals about PTU's hepatotoxicity in June 2009 and has added the boxed warning as part of the Risk Evaluation and Mitigation Strategy (REMS) for the drug.

There were 34 cases of severe liver injury associated with PTU reported between 1969 and 2009. The FDA is requiring a boxed warning because of the severity of these cases “and to ensure

that healthcare professionals are aware of this risk and are vigilant for the signs and symptoms of hepatic toxicity,” the statement added.

### Rules for Home Use Strengthened

Citing reports of injuries and deaths associated with home use of medical devices that may not have been intended for use in that environment, the FDA announced that it will enhance its regulation of such products.

The agency aims to have a final policy in place within a year. Devices targeted by this initiative include cardiac

monitors, ventilators, infusion pumps, dialysis machines, and wound-care products.

The FDA receives about 1,500 reports of adverse events occurring in homes each year. It is not clear how many of those are related to home use of medical devices; however, the agency has become increasingly concerned based on the trend toward early hospital discharge as well as aging of the population.

Among the types of events reported were ventilator failure because a caregiver did not hear an alarm; cat dander clogging a dialysis machine; and video-

game interference causing the malfunction of implantable cardioverter defibrillators.

About 8 million people receive home care each year from 17,000 paid providers, at a cost of about \$57 billion. Those figures don't account for people who receive care from family members.

The FDA will establish a multipronged approach to ensuring that manufacturers, home health agencies, patients, and caregivers have the information needed to reduce the risk of malfunctions, injuries, and deaths.

—From staff reports

I have type 2 diabetes. This is... my 24/7 glucose control

Covered on more than 90% of managed care plans!

Model is for illustrative purposes only.

#### Indications and usage

Levemir® is indicated for once- or twice-daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

#### Important safety information

Levemir® is contraindicated in patients hypersensitive to insulin detemir or one of its excipients.

Hypoglycemia is the most common adverse effect of all insulin therapies, including Levemir®. As with other insulins, the timing of hypoglycemic events may differ among various insulin preparations. Glucose monitoring is recommended for all patients with diabetes. Levemir® is not to be used in insulin infusion pumps. Any change of insulin dose should be made cautiously and only under medical supervision. Concomitant oral antidiabetic treatment may require adjustment.

Inadequate dosing or discontinuation of treatment may lead to hyperglycemia and, in patients with type 1 diabetes, diabetic ketoacidosis. Levemir® should not be diluted or mixed with any

other insulin preparations. Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy. Dose and timing of administration may need to be adjusted to reduce the risk of hypoglycemia in patients being switched to Levemir® from other intermediate or long-acting insulin preparations. The dose of Levemir® may need to be adjusted in patients with renal or hepatic impairment.

Other adverse events commonly associated with insulin therapy may include injection site reactions (on average, 3% to 4% of patients in clinical trials) such as lipodystrophy, redness, pain, itching, hives, swelling, and inflammation.

\*Whether these observed differences represent true differences in the effects of Levemir®, NPH insulin, and insulin glargine is not known, since these trials were not blinded and the protocols (eg, diet and exercise instructions and monitoring) were not specifically directed at exploring hypotheses related to weight effects of the treatments compared. The clinical significance of the observed differences in weight has not been established.

For your patients with type 2 diabetes, start once-daily Levemir®

Levemir® helps patients with diabetes achieve their A1C goal.<sup>2,3</sup>

- 24-hour action at a once-daily dose<sup>4,5</sup>
- Provides consistent insulin absorption and action, day after day<sup>4,6,7</sup>
- Less weight gain<sup>8\*</sup>

To access complimentary e-learning programs, visit [novomedlink.com/Levemir](http://novomedlink.com/Levemir)

**References:** 1. Data on file. Novo Nordisk Inc, Princeton, NJ. 2. Meneghini LF, Rosenberg KH, Koenen C, Meriläinen MJ, Lüddeke H-J. Insulin detemir improves glycaemic control with less hypoglycaemia and no weight gain in patients with type 2 diabetes who were insulin naive or treated with NPH or insulin glargine: clinical practice experience from a German subgroup of the PREDICTIVE study. *Diabetes Obes Metab*. 2007;9(3):418-427. 3. Hermansen K, Davies M, Dereziński T, Ravn GM, Clauson P, Home P, for the Levemir Treat-to-Target Study Group. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naïve people with type 2 diabetes. *Diabetes Care*. 2006;29(6):1269-1274. 4. Klein O, Lyngé J, Endahl L, Damholt B, Nosek L, Heise T. Albumin-bound basal insulin analogues (insulin detemir and NN344): comparable time-action profiles but less variability than insulin glargine in type 2 diabetes. *Diabetes Obes Metab*. 2007;9(3):290-299. 5. Philis-Tsimikas A, Charpentier G, Clauson P, Ravn GM, Roberts VL, Thorsteinsson B. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. *Clin Ther*. 2006;28(10):1569-1581. 6. Danne T, Endahl L, Haahr H, et al. Lower within-subject variability in pharmacokinetic profiles of insulin detemir in comparison to insulin glargine in children and adolescents with type 1 diabetes. Presented at: 43rd Annual Meeting of the European Association for the Study of Diabetes; September 17-21, 2007; Amsterdam, Netherlands. Abstract 0189. 7. Heise T, Nosek L, Ronn BB, et al. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. *Diabetes*. 2004;53(6):1614-1620. 8. Data on file. NDA21-536. Novo Nordisk Inc, Princeton, NJ.



**Levemir®**  
insulin detemir (rDNA origin) injection



Please see brief summary of Prescribing Information on adjacent page.

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November 2008