

## POLICY & PRACTICE

### Bergenstal Elected to ADA Post

Dr. Richard M. Bergenstal is the new vice president for medicine and science at the American Diabetes Association. Dr. Bergenstal, a researcher who focuses on the link between glucose control and diabetes complications, previously served on the ADA's board of directors as well as several association committees. He also previously chaired the association's Council on Clinical Endocrinology, Health Care Delivery, and Public Health. Dr. Bergenstal is executive director of the International Diabetes Center at Park Nicollet in Minneapolis and clinical professor of medicine at the University of Minnesota.

### Questions About BTC Drugs

The House Energy and Commerce Committee is investigating the wisdom of behind-the-counter drug dispensing. The committee has asked the Government Accountability Office to update a study it conducted in 1995, "Nonprescription Drugs: Value of a Pharmacist-Controlled Class Has Yet to Be Demonstrated." At a November public meeting on the subject, the agency said it had no intention of establishing a new BTC class in the immediate future.

### Scant Number of New Approvals

The FDA approved only 17 new molecular entities (NMEs) in 2007, the lowest number since 2002. This comes on the heels of 2 previous years with only 18 NME approvals each. NMEs are unique products. Those approved in 2007 included two HIV therapies, four oncology products, two antihypertensives, one antibiotic, and one each to treat Parkinson's disease, pulmonary hypertension, impetigo, acromegaly, attention-deficit hyperactivity disorder, and phenylketonuria. Also approved were an imaging agent and injection to prevent blood volume loss during surgery, a handful of biologics, an influenza vaccine, and an avian flu vaccine.

### Docs Mistrust Error Reporting Systems

U.S. physicians are willing to report medical errors but don't trust the current error reporting systems, according to a study in the January/February issue of Health Affairs. Between July 2003 and March 2004, researchers surveyed more than 1,000 physicians in rural and urban areas of Missouri and Washington state. They found that because of their mistrust of current systems, most physicians rely on informal discussion with colleagues as a way to report and share information about errors. Most physicians also reported that they had been involved in an error—56% with a serious error, 74% with a minor error, and 66% with a "near miss." When asked what would increase their willingness to formally report errors, 88% said they wanted information to be kept confidential and nondiscoverable, 85% wanted evidence that error information would be used for system improvements, and 53% said they wanted review activities confined to their department. "These findings shed light on an important question—how to create error-reporting programs that will encourage clinician participation," said Dr. Carolyn M. Clancy, director of the Agency for Healthcare Research and Quality, which

funded the study. "Physicians say they want to learn from errors that take place in their institution. We need to build on that willingness with error-reporting programs that encourage their participation."

### Judge Overturns Rx Info Law

A federal judge has overturned a Maine law that would have restricted medical data companies' access to physician prescribing information. In a decision that relied heavily on a previous ruling in New Hampshire, U.S. District Judge John Woodcock said that the law would prohibit "the transfer

of truthful commercial information" and would violate the free speech guarantee of the First Amendment. The Maine law was challenged on constitutional grounds by IMS Health, Wolters Kluwer Health, and Verispan, all medical data companies that collect, analyze, and sell such data to pharmaceutical manufacturers. The companies also argued that the law bucks a national trend toward greater transparency in health care information.

### FDA Cancels DTC User Fee Program

The Food and Drug Administration recently announced that it is pulling the plug on a voluntary user fee program for direct-

to-consumer television advertisements. The agency had planned to charge pharmaceutical companies about \$40,000 per ad to review their DTC television spots. But in January, the FDA issued a notice saying that it would not go forward with the user fee program because no money was appropriated for the program in the fiscal year 2008 consolidated appropriations bill. Under the law that authorized the program, the agency can collect fees only up to the amount provided in advance by congressional appropriations. As a result, the FDA plans to review any ads already submitted at no charge, as resources will allow.

—Joyce Frieden

## Levemir® insulin detemir (rDNA origin) injection

**Rx ONLY**  
**BRIEF SUMMARY. Please see package insert for prescribing information.**

#### 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.

#### CONTRAINDICATIONS

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

#### WARNINGS

**Hypoglycemia is the most common adverse effect of insulin therapy, including LEVEMIR. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations.**

**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. Changes in insulin strength, timing of dosing, manufacturer, type (e.g., regular, NPH, or insulin analogs), species (animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted.**

#### PRECAUTIONS

##### General

Inadequate dosing or discontinuation of treatment may lead to hyperglycemia and, in patients with type 1 diabetes, diabetic ketoacidosis. The first symptoms of hyperglycemia usually occur gradually over a period of hours or days. They include nausea, vomiting, drowsiness, flushed dry skin, dry mouth, increased urination, thirst and loss of appetite as well as acetone breath. Untreated hyperglycemic events are potentially fatal.

LEVEMIR is not intended for intravenous or intramuscular administration. The prolonged duration of activity of insulin detemir is dependent on injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia. Absorption after intramuscular administration is both faster and more extensive than absorption after subcutaneous administration.

**LEVEMIR should not be diluted or mixed with any other insulin preparations** (see PRECAUTIONS, Mixing of Insulins).

Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Lipodystrophy and hypersensitivity are among potential clinical adverse effects associated with the use of all insulins.

As with all insulin preparations, the time course of LEVEMIR action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan.

##### Hypoglycemia

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of LEVEMIR. Hypoglycemia is the most common adverse effect of insulins. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control (see PRECAUTIONS, Drug Interactions). Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to patients' awareness of hypoglycemia.

The time of occurrence of hypoglycemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen or timing of dosing is changed. In patients being switched from other intermediate or long-acting insulin preparations to once- or twice-daily LEVEMIR, dosages can be prescribed on a unit-to-unit basis; however, as with all insulin preparations, dose and timing of administration may need to be adjusted to reduce the risk of hypoglycemia.

##### Renal Impairment

As with other insulins, the requirements for LEVEMIR may need to be adjusted in patients with renal impairment.

##### Hepatic Impairment

As with other insulins, the requirements for LEVEMIR may need to be adjusted in patients with hepatic impairment.

##### Injection Site and Allergic Reactions

As with any insulin therapy, lipodystrophy may occur at the injection site and delay insulin absorption. Other injection site reactions with insulin therapy may include redness, pain, itching, hives, swelling, and inflammation. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Reactions usually resolve in a few days to a few

weeks. On rare occasions, injection site reactions may require discontinuation of LEVEMIR.

In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic allergy: Generalized allergy to insulin, which is less common but potentially more serious, may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life-threatening.

##### Intercurrent Conditions

Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances, or other stresses.

##### Information for Patients

LEVEMIR must only be used if the solution appears clear and colorless with no visible particles. Patients should be informed about potential risks and advantages of LEVEMIR therapy, including the possible side effects. Patients should be offered continued education and advice on insulin therapies, injection technique, life-style management, regular glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, adherence to meal planning, complications of insulin therapy, timing of dosage, instruction for use of injection devices and proper storage of insulin. Patients should be informed that frequent, patient-performed blood glucose measurements are needed to achieve effective glyemic control to avoid both hyperglycemia and hypoglycemia. Patients must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, or skipped meals. Refer patients to the LEVEMIR "Patient Information" circular for additional information.

As with all patients who have diabetes, the ability to concentrate and/or react may be impaired as a result of hypoglycemia or hyperglycemia.

Patients with diabetes should be advised to inform their health care professional if they are pregnant or are contemplating pregnancy (see PRECAUTIONS, Pregnancy).

##### Laboratory Tests

As with all insulin therapy, the therapeutic response to LEVEMIR should be monitored by periodic blood glucose tests. Periodic measurement of HbA<sub>1c</sub> is recommended for the monitoring of long-term glyemic control.

##### Drug Interactions

A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

The following are examples of substances that may reduce the blood-glucose-lowering effect of insulin: corticosteroids, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives).

The following are examples of substances that may increase the blood-glucose-lowering effect of insulin and susceptibility to hypoglycemia: oral antidiabetic drugs, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), and sulfonamide antibiotics.

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia. In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent.

The results of *in-vitro* and *in-vivo* protein binding studies demonstrate that there is no clinically relevant interaction between insulin detemir and fatty acids or other protein bound drugs.

##### Mixing of Insulins

If LEVEMIR is mixed with other insulin preparations, the profile of action of one or both individual components may change. Mixing LEVEMIR with insulin aspart, a rapid acting insulin analog, resulted in about 40% reduction in AUC<sub>(0-2h)</sub> and C<sub>max</sub> for insulin aspart compared to separate injections when the ratio of insulin aspart to LEVEMIR was less than 50%.

**LEVEMIR should NOT be mixed or diluted with any other insulin preparations.**

##### Carcinogenicity, Mutagenicity, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed. Insulin detemir tested negative for genotoxic potential in the *in-vitro* reverse mutation study in bacteria, human peripheral blood lymphocyte chromosome aberration test, and the *in-vivo* mouse micronucleus test.

##### Pregnancy: Teratogenic Effects: Pregnancy Category C

In a fertility and embryonic development study, insulin detemir was administered to female rats before mating, during mating, and throughout pregnancy at doses up to 300 nmol/kg/day (3 times the recommended human dose, based on plasma Area Under the Curve (AUC) ratio). Doses of 150 and 300 nmol/kg/day produced numbers of litters with visceral anomalies. Doses up to 900 nmol/kg/day (approximately 135 times the recommended human dose based on AUC ratio) were given to rabbits during organogenesis. Drug-dose related increases in the incidence of fetuses with gall bladder abnormalities such as small, bilobed, bifurcated and missing gall bladders were observed at a dose of 900 nmol/kg/day. The rat and rabbit embryofetal development studies that included concurrent human insulin control groups

indicated that insulin detemir and human insulin had similar effects regarding embryotoxicity and teratogenicity.

##### Nursing mothers

It is unknown whether LEVEMIR is excreted in significant amounts in human milk. For this reason, caution should be exercised when LEVEMIR is administered to a nursing mother. Patients with diabetes who are lactating may require adjustments in insulin dose, meal plan, or both.

##### Pediatric use

In a controlled clinical study, HbA<sub>1c</sub> concentrations and rates of hypoglycemia were similar among patients treated with LEVEMIR and patients treated with NPH human insulin.

##### Geriatric use

Of the total number of subjects in intermediate and long-term clinical studies of LEVEMIR, 85 (type 1 studies) and 363 (type 2 studies) were 65 years and older. 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. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly.

##### ADVERSE REACTIONS

Adverse events commonly associated with human insulin therapy include the following:

**Body as Whole:** allergic reactions (see PRECAUTIONS, Allergy).

**Skin and Appendages:** lipodystrophy, pruritus, rash. Mild injection site reactions occurred more frequently with LEVEMIR than with NPH human insulin and usually resolved in a few days to a few weeks (see PRECAUTIONS, Allergy).

##### Other:

**Hypoglycemia:** (see WARNINGS and PRECAUTIONS).

In trials of up to 6 months duration in patients with type 1 and type 2 diabetes, the incidence of severe hypoglycemia with LEVEMIR was comparable to the incidence with NPH, and, as expected, greater overall in patients with type 1 diabetes (Table 4).

##### Weight gain:

In trials of up to 6 months duration in patients with type 1 and type 2 diabetes, LEVEMIR was associated with somewhat less weight gain than NPH (Table 4). Whether these observed differences represent true differences in the effects of LEVEMIR and NPH insulin is not known, since these trials were not blinded and the protocols (e.g., 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 has not been established.

**Table 4: Safety Information on Clinical Studies**

Table 4: Safety information for clinical studies						
Treatment	# of subjects	Weight (kg)		Hypoglycemia (events/subject/month)		
		Baseline	End of treatment	Major*	Minor	
<b>Type 1</b>						
Study A	LEVEMIR	N=276	75.0	75.1	0.045	2.184
	NPH	N=133	75.7	76.4	0.035	3.063
Study C	LEVEMIR	N=492	76.5	76.3	0.029	2.397
	NPH	N=257	76.1	76.5	0.027	2.564
Study D	LEVEMIR	N=232	N/A	N/A	0.076	2.677
	Pediatric	N=115	N/A	N/A	0.083	3.203
<b>Type 2</b>						
Study E	LEVEMIR	N=237	82.7	83.7	0.001	0.306
	NPH	N=239	82.4	85.2	0.006	0.595
Study F	LEVEMIR	N=195	81.8	82.3	0.003	0.193
	NPH	N=200	79.6	80.9	0.006	0.235

\* Major = requires assistance of another individual because of neurologic impairment

\*\* Minor = plasma glucose <56 mg/dl, subject able to deal with the episode him/herself

##### OVERDOSAGE

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/ subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid reoccurrence of hypoglycemia.

**More detailed information is available on request.**

##### Rx only

Date of issue: October 19, 2005

Manufactured for Novo Nordisk Inc., Princeton, NJ 08540

Manufactured by Novo Nordisk A/S, 2880 Bagsvaerd, Denmark

www.novonordisk-us.com

Levemir® and Novo Nordisk® are trademarks of Novo Nordisk A/S.

© 2006 Novo Nordisk Inc.

130128R

May 2006

