

# Accutane Program Remains a Work in Progress

BY CHRISTINE KILGORE  
Contributing Writer

**D**ermatologists and their patients taking isotretinoin are entering the second year of the iPLEDGE mandatory risk management program aimed at preventing isotretinoin-related teratogenicity, and the specialty's leaders on the issue are anticipating further improvement in a system they say remains poorly designed.

"It's safe to say that within the first half of 2007, probably in later spring, there should be additional program improvement. ... More improvement is coming," said Dr. Diane Thiboutot, former chair of the American Academy of Dermatology task force on isotretinoin.

What is not clear, however—and won't be for at least another year—is the impact the program is having on the prevention of pregnancies in women taking the teratogenic drug.

Both Dr. Thiboutot, who will continue serving on the task force, and Dr. Susan Walker, who became the director of the Food and Drug Administration's Division of Dermatology and Dental Products last June, said for the first time in February that there is "preliminary" evidence that the program is reducing the number of women who are pregnant at the time they start isotretinoin therapy.

But they offered no details, and Dr. Thiboutot explained that the manufacturers

now plan to use data from the first full year of iPLEDGE "as baseline data" for comparison with pregnancy data collected during the entire second year. Before iPLEDGE was implemented, the pregnancy rate in women taking isotretinoin (Accutane) was about 4 per 1,000 women, she said.

"In the interim, some sort of methodology [for evaluating success of the program] will be determined," said Dr. Thiboutot, professor of dermatology at Pennsylvania State University, Hershey.

The most significant change to come this year, in the meantime, will likely be an elimination of the 23-day lockout period for women of childbearing potential. With such a rule change, women who do not have their prescriptions filled within 7 days could undergo another pregnancy test and office visit and then get a refill without having to wait 23 days.

The FDA eliminated this lockout period last October for males and females of non-childbearing potential, while promising

## 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 glycemic 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 glycemic 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**

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 recurrence of hypoglycemia.

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

#### Rx only

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**The iPLEDGE program 'is definitely running light-years better' than it did at the start.**

**DR. DEL ROSSO**

that a change in this rule for females of childbearing potential would be "rolled out" in 2007 (INTERNAL MEDICINE NEWS, Dec. 1, 2006, p. 11).

A spokesperson for Covance, the Princeton, N.J.-based company that manages iPLEDGE, confirmed that the firm is "working on eliminating [the lockout]."

Dr. Thiboutot said she and other AAD leaders have been pushing for other changes as well—for instance, the incorporation of specific dates rather than time windows in the iPLEDGE online program—based on input from dermatologists who have communicated with the academy as well as a survey of 400 dermatologists taken this summer. The poll showed that 95% were prescribing isotretinoin and that 90% of them were having difficulty with the iPLEDGE program.

Dr. Stephen Stone, who recently assumed the chairmanship of the academy's task force on isotretinoin, said the academy has a "seat at the table" that it did not have as iPLEDGE was being designed and implemented.

"The FDA is definitely listening to us," said Dr. Stone, immediate past president of the AAD and professor of clinical medicine at Southern Illinois University, Springfield. "My understanding is that iPLEDGE will be improved, at least in its ease of application."

Even with the elimination of the 23-day lockout period for men and women of nonchildbearing potential, "participation of these patients in the system is still overly complicated," he said. "There still [needs to be] some liberalization of rules."

Dermatologists still are debating the program's effects on prescribing. Dr. Noah

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Scheinfeld, of the dermatology department of Columbia University, New York, estimated last spring that prescribing in his region had dropped by at least 50%. That estimate still holds true, he said.

Dr. Elaine Siegfried, a dermatologist at St. Louis University who chairs the AAD's Environment and Drugs Committee, said, on the other hand, that the number of isotretinoin prescriptions dropped after implementation of iPLEDGE but now appears to be back up to approximately where it was under the voluntary SMART (System to Manage Accutane-Related Teratogenicity) program.

(The total number of prescriptions dispensed in the United States in the year after SMART was implemented had declined 23% from the previous year.)

According to Covance's data, while the number of prescribers and pharmacies activated has remained about the same in the last 6 months, the number of patients activated in the program has risen significantly, from 140,000 patients last June to more than 244,000 in December.

Calls to the AAD office, meanwhile, have continued to decline—a trend that AAD leaders say likely reflects changes made by Covance in the spring (the company added staff to its call center and made changes to its Web site, for instance, resolving some of the program's operational difficulties), as well as time needed to learn the system and delegate responsibility.

The average wait time for getting help from the iPLEDGE call center in December was 2 minutes, according to Covance spokesperson Laurene Isip.

"The program is definitely running light-years better" than it did at the start, said Dr. James Del Rosso, of the department of dermatology at University of Nevada, Reno, and immediate past chairman of the AAD's Environment and Drugs Committee.

Dr. Sharon Gardepe, who has a solo practice in general dermatology in Huntsville, Ala., called her legislators and the AAD soon after implementation about her concerns and experience with iPLEDGE. She also created a handout listing local legislators to give to her patients who complained about the program. "Giving them the list underlined the fact that it wasn't me," she said.

One year into the program, Dr. Gardepe said her hour-long phone calls to Covance are a thing of the past, but the requirement that prescriptions be picked up within 7 days and the rule that lab tests be conducted no sooner than 1 day before the office visit still result in "a lot of time spent troubleshooting."

"Some people are optimistic that we might be better able to work with [FDA and Covance], but I'm still skeptical" about the extent of future change, she said.

Dr. Siegfried said such skepticism is understandable. "I really am optimistic. I do think that Dr. Walker [at the FDA] wants to build bridges," she said. "But in the end it's not her call—it's Congress."

Dr. Siegfried and other AAD leaders urge physicians to remain vigilant and active. Isotretinoin, they caution, will likely be in the limelight this year, since Rep. Bart Stupak (D-Mich.) has announced that he wants to hold a congressional hearing

on the FDA's management of the drug.

Dr. Siegfried said that she believes the decision to collect a full year of baseline data and then another year of comparison data before reporting pregnancy rates—rather than releasing iPLEDGE data quarterly, as was first anticipated—reflects the realization that "if the data were made public [along the way], and there's been one pregnancy, it will haunt us and we won't have the drug [at all]."

Dr. Stone said he too is concerned, saying that iPLEDGE "will minimize the number of pregnancies by forcing people to go through the hoops, but I don't think we'll ever eliminate pregnancies." ■

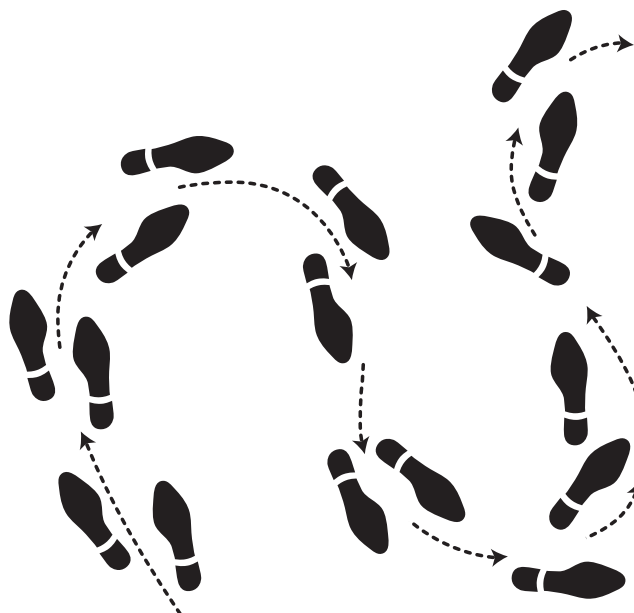


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Dr. Elaine Siegfried, a dermatologist at St. Louis University who chairs the AAD's Environment and Drugs Committee, said isotretinoin prescriptions dropped after implementation of iPLEDGE but now are back up.

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**IMPORTANT SAFETY INFORMATION ABOUT MIRAPEX: Patients have reported falling asleep without perceived warning signs during activities of daily living, including operation of a motor vehicle.** Hallucinations and postural (orthostatic) hypotension may occur. The most commonly reported adverse events in RLS clinical trials for MIRAPEX vs placebo were nausea (16% vs 5%), headache (16% vs 15%), fatigue (9% vs 7%), and somnolence (6% vs 3%).

Patients and caregivers should be informed that impulse control disorders/compulsive behaviors may occur while taking medicines, including pramipexole, to treat Parkinson's disease and RLS.

Please see accompanying Brief Summary of Prescribing Information.

\*Results of a 12-week, placebo-controlled, randomized, double-blind, fixed-dose-treatment trial to assess the efficacy and safety of MIRAPEX vs placebo in the treatment of moderate to severe primary RLS (MIRAPEX n=254; placebo n=85). Measurement parameters included the International Restless Legs Syndrome Rating Scale (IRLS) and the Clinical Global Impressions-Improvement (CGI-I) scale. IRLS is an internationally validated scale that is the standard instrument for evaluation of severity of RLS. Total score ranges from 0 to 40, with 0 being absence of RLS symptoms and 40 the most severe symptoms. CGI-I is widely accepted for measuring improvement in RLS symptoms.

Reference: 1. Data on file, Boehringer Ingelheim Pharmaceuticals, Inc.

