

# Incentives Called For to Fill Antibiotic Pipeline

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"The Pink Sheet"

FROM A HEARING OF THE HOUSE ENERGY AND COMMERCE COMMITTEE, SUBCOMMITTEE ON HEALTH

WASHINGTON — Government incentives probably will be necessary to rejuvenate the drug development pipeline for antibiotics, Dr. Janet Woodcock, chief medical officer of the Food and Drug Administration, testified before a con-

gressional committee.

The number of investigational new drug applications for antibiotics has declined since 1987 but has started to increase again over the last 3 years, Dr. Woodcock told the House Energy and Commerce Committee, Subcommittee on Health. But as more bacteria develop resistance to antibiotics, more and new therapies are necessary, she added.

Drug-resistant infections cost \$35 bil-

lion a year in the United States, yet many companies do not find antibiotics a financially viable product since they involve a limited course of treatment and have generic competition, among other factors.

There also is confusion among the scientific pathway for approval. Dr. Woodcock said that new guidance documents on clinical trial designs are in the works but acknowledged that they may

not be enough to push the industry to increase drug development.

"It will likely also take the development of incentives in order to stimulate the development of new antibacterial drugs so that we have new therapeutic options" to treat current and future resistant pathogens, Dr. Woodcock said in written testimony.

Recognizing that government intervention is necessary to help solve the problem is a giant step forward, said Dr. Barry Eisenstein, senior vice president of scientific affairs at Cubist Pharmaceuticals, who also testified at the hearing.

Cubist currently markets daptomycin (Cubicin) for the treatment of skin and skin structure infections caused by certain susceptible strains of gram-positive microorganisms, including methicillin-resistant *Staphylococcus aureus* (MRSA). The company currently has three antibiotic drugs in development, he said.

"To me, this is almost a breakthrough to see a branch of government actually saying, 'You know what? We really do have market failure, we need government intervention in a meaningful way,'" Dr. Eisenstein said in an interview.

In his testimony, Dr. Eisenstein supported policies for antibiotics modeled on the programs that have sparked development of drugs for rare diseases and expanded the knowledge about pediatric uses.

"New incentives must be designed so that they encourage investment in activities across the research spectrum, from basic research to clinical trials, and target as broad a range of scientists, entrepreneurs, large and small companies, and life science investors as possible," Dr. Eisenstein said in written testimony.

Dr. Woodcock warned that incentives still have to be considered in the context of restrictions that may be required once the drugs are on the market because the ultimate goal is limiting antibiotic use.

"If we contemplated a pipeline that would end up [where] antimicrobials would only be used in niche situations, where they were really needed, that would be even a further disincentive," she said. "But you have to think about that as a goal to preserve the effect of that for a long time."

Robin Robinson, Ph.D., director of the Department of Health and Human Services' Biomedical Advanced Research and Development Authority, said that industry has indicated in the past that liability protections would be very helpful and important in moving drugs along the pipeline.

Dr. Robinson and Dr. Woodcock also said that easing antitrust laws in certain cases to encourage companies to work together was worth exploring. Dr. Robinson noted that BARDA used that authority in the development of the H5N1 and H1N1 influenza vaccines, and certainly could try it again. ■

## Levemir® (insulin detemir [rDNA origin] injection)

### Rx ONLY

#### BRIEF SUMMARY. Please see package insert for full 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. Needles and LEVEMIR® FlexPen® must not be shared.**

**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     | NPH       | 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    |

\* See CLINICAL STUDIES section for description of individual studies  
 \*\* 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 upon request.**

Date of Issue: July 15, 2009

Version: 5

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Manufactured for: Novo Nordisk Inc., Princeton, NJ 08540, www.novonordisk-us.com

Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark

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