

## BUSINESS BRIEFS

### Sanofi Seals Deal for Monitors

Sanofi-Aventis will codevelop blood glucose monitoring devices with the French pharmaceutical company AgaMatrix in a deal that could provide leverage to Sanofi if it pursues agreements with larger partners in the diabetes arena, said David Kliff, founder of the Web site Diabetic Investor. AgaMatrix will develop a portfolio of glucose monitors exclusively for Sanofi, benefiting in return from Sanofi's global brands and marketing reach. Sanofi executives predicted that the addition of blood glucose monitors and insulin pumps would give the company's diabetes business a competitive edge. Lantus, Sanofi's long-acting insulin, brought in \$4.6 billion in sales last year, and Apidra, its short-acting insulin, yielded \$185 million. Providing a system connecting pharma products, devices, and patient education "is the way diabetes management is going," Mr. Kliff said.

### Forest Labs, Phenomix Split

Forest Laboratories Inc. of New York has ended its agreement with Phenomix Corp. in San Diego to develop and market dutogliptin for type 2 diabetes. Forest canceled the agreement "for business reasons," according to its quarterly earnings report. The \$340 million deal, initiated in the fall of 2008, provided Phenomix \$75 million up front and split the development and commercialization costs between the two companies. Phenomix' phase III trial demonstrated that dutogliptin met its primary goal of lowering hemoglobin A<sub>1c</sub> levels. "We are disappointed that on the heels of such positive data that we will not be moving forward with our collaboration with Forest," said Laura Shawver, Phenomix's chief executive officer.

### Alimera Misses IPO Target

Alimera Sciences, which is developing drugs for ophthalmic diseases, raised \$72 million at \$11 a share in its IPO last month. The company had targeted a \$96 million IPO with shares priced at \$15-\$17, but incurred 2009 operating expenses of \$19 million and debt of nearly \$48 million. Some of the funds will be used to pay debts to pSivida, an Australian company that acquired Control Delivery Systems, which had partnered with Alimera to develop lluvien for diabetic macular edema. Alimera also will spend about \$13.4 million to finish phase III trials of the drug. If the drug gains Food and Drug Administration approval, Alimera will have to make a \$25 million milestone payment to pSivida. Based in Alpharetta, Ga., Alimera had raised \$88.6 million as of July 2008 in previous funding rounds. "If we are not successful in commercializing lluvien... our business will be materially harmed and we may need to curtail or cease operations," the company reported in a filing.

### Charles River Nabs Chinese Firm

Charles River Laboratories International, based in Wilmington, Mass., will buy WuXi PharmaTech of Shanghai, China, for \$1.6 billion. The proposed combination would allow drug developers to

conduct preclinical studies in the United States, Europe, and China. The acquisition, through a combined cash and stock transaction, would provide a premium of at least 28% to the closing price of WuXi's stock on the New York Stock Exchange as of April 23, according to executives at both companies. "Outsourcing seems to be an inexorable trend," said Ge Li, WuXi's founder and CEO. James Foster, CEO of Charles River, agreed, citing lower costs and the availability of trained scientists in China. The merger,

## 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**  
**Hyperglycemia is the most common adverse effect of insulin therapy, including LEVEMIR. As with all insulins, the timing of hyperglycemia 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.

##### Hyperglycemia

As with all insulin preparations, hyperglycemic reactions may be associated with the administration of LEVEMIR. Hyperglycemia is the most common adverse effect of insulins. Early warning symptoms of hyperglycemia 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 hyperglycemia.

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

sales momentum, according to a company statement. Under his leadership, Merck launched a new commercial model in the United States and in key markets in Europe, Latin America, and Asia Pacific; improved the division structure; and expanded the company's reach in emerging markets, the statement noted. As part of a restructuring program to reduce costs by \$3 billion, the company plans to reduce its workforce by 15% by 2012.

—From staff reports

Reporters and editors from Elsevier's "The Pink Sheet" contributed to this column.

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	Baseline	End of treatment	Weight (kg)		Hypoglycemia (events/subject/month)	
				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	
	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	

\* 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

Hyperglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Mild episodes of hyperglycemia 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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