

Senate Passes Renewal of Rx Drug User Fee Act

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After some last-minute wrangling over drug reimportation and regulation of advertising, the Senate voted 93-1 to fund another 5 years of the Prescription Drug User Fee Act.

Among other issues, PDUFA governs how much pharmaceutical manufacturers pay to have their products reviewed by the Food and Drug Administration, and how

quickly the agency must complete those reviews.

The current PDUFA law expires Sept. 30. Some have criticized the program, saying that it lets a regulated industry have too much power over its regulators. But the FDA has become increasingly dependent on user fees to fund its work.

At least one amendment (S. 1082) that was successfully attached to the original legislation would give the agency more teeth. Senators voted 64-30 to approve

Sen. Chuck Grassley's (R-Iowa) amendment to increase fines—from \$10,000 to \$250,000—for companies that don't comply with FDA directives on label changes, postapproval studies, and communicating new information about safety.

The penalties would double every 30 days, but would be capped at \$2 million.

"These penalties need to be more than just an insignificant cost of doing business in order to affect behavior," said Sen. Grassley in a statement.

Drug safety has been a significant focus of the legislation as it has made its way through the Senate.

Sen. Edward Kennedy (D-Mass.) and Sen. Michael Enzi (R-Wy.) had been hoping to attach proposals for improved drug safety to the PDUFA reauthorization, but most of their suggestions were defeated or watered down in a committee vote in mid-April.

The centerpiece of their proposals was to require a risk evaluation and mitigation strategy (REMS) plan for all new chemical entities and biologics. Instead, the Senate Health, Education, Labor, and Pensions committee voted to give the FDA authority to determine when a new drug should have a REMS. That provision made it into the legislation that passed the full Senate. The panel also voted to require the FDA to set up a public-private partnership for routine surveillance of postmarketing drug safety, which also was part of the final bill.

PDUFA would allow the FDA to collect \$393 million in drug user fees in 2008, including a \$30-million increase for postapproval drug safety programs.

The bill would also require drug makers to publish a registry of all late-phase II and all phase III and IV trials, and to make all trial results available in a public database.

Finally, PDUFA would fund another 5 years of the Best Pharmaceuticals for Children Act. Companies that conduct pediatric studies of their products are eligible for additional patent life under the law, which expires Oct. 1. The new 5-year program will extend a drug's patent life by 3 months (instead of 6 offered under the previous law) if sales of the product are more than \$1 billion, and by 6 months if sales are less than \$1 billion.

Under the Best Pharmaceuticals for Children Act, the Government Accountability Office found that drug sponsors have initiated pediatric drug studies for most of the on-patent drugs for which the FDA has requested studies. About 87% of drugs studied had labeling changes, often because the pediatric drug studies found that children might have been exposed to ineffective drugs or dosing, overdosing, or previously unknown side effects.

The federal government can order manufacturers to conduct pediatric studies, but that almost never happens because the bureaucratic hurdles for making such a request are so high. The PDUFA reauthorization aims to streamline the process.

The Senate vote was hailed by the brand-name and generic pharmaceutical industries.

"The significant increases in user fees will provide the FDA the resources necessary to improve and modernize its already strong drug safety monitoring system," PhRMA President and CEO Billy Tauzin said in a statement.

The generic industry was happy because it secured a promise from a group of senators to mark up legislation authorizing generic copies of biologic drugs by mid-June, with a goal of incorporating it into the final House-Senate agreement on the PDUFA law.

The PDUFA legislation still has far to go before it becomes law. The House is still in the early phases of work. ■

References: 1. Brange J, Volund A. Insulin analogs with improved pharmacokinetic profiles. *Adv Drug Deliv Rev.* 1999;35:307-355. 2. Raskin P, Guthrie RA, Leiter L, Riis A, Jovanovic L. Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. *Diabetes Care.* 2000;23:583-588. 3. Niskanen L, Jensen LE, Råstam J, Nygaard-Pedersen L, Erichsen K, Vora JP. Randomized, multinational, open-label, 2-period, crossover comparison of biphasic insulin aspart 30 and biphasic insulin lispro 25 and pen devices in adult patients with type 2 diabetes mellitus. *Clin Ther.* 2004;26:531-540.

NovoLog®

Insulin aspart (rDNA origin) injection

100 units of insulin aspart per mL (U-100)

3 mL NovoLog® FlexPen® prefilled syringe

10 mL vials

3 mL PenFill® cartridges are for use with compatible insulin delivery devices and the NovoPen® 3 PenMate®.

BRIEF SUMMARY. PLEASE CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

INDICATIONS AND USAGE

NovoLog is indicated for the treatment of patients with diabetes mellitus, for the control of hyperglycemia. Because NovoLog has a more rapid onset and a shorter duration of activity than human regular insulin, NovoLog given by injection should normally be used in regimens with an intermediate or long-acting insulin. NovoLog may also be infused subcutaneously by external insulin pumps. NovoLog may be administered intravenously under proper medical supervision in a clinical setting for glycemic control. (See WARNINGS; PRECAUTIONS [especially Usage in Pumps], Mixing of Insulins.)

CONTRAINDICATIONS

NovoLog is contraindicated during episodes of hypoglycemia and in patients hypersensitive to NovoLog or one of its excipients.

WARNINGS

NovoLog differs from regular human insulin by a more rapid onset and a shorter duration of activity. Because of the fast onset of action, the injection of NovoLog should immediately be followed by a meal. Because of the short duration of action of NovoLog, patients with diabetes also require a longer-acting insulin to maintain adequate glucose control. Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using external pump infusion therapy.

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

Any change of insulin dose should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (e.g., regular, NPH, analog), species (animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

Insulin Pumps - When used in an external insulin pump for subcutaneous infusion, NovoLog should not be diluted or mixed with any other insulin. Physicians and patients should carefully evaluate information on pump use in the NovoLog physician and patient package inserts and in the pump manufacturer's manual (e.g., NovoLog-specific information should be followed for in-use time, frequency of changing infusion sets, or other details specific to NovoLog usage, because NovoLog-specific information may differ from general pump manual instructions).

Pump or infusion set malfunctions or insulin degradation can lead to hyperglycemia and ketosis in a short time because of the small subcutaneous depot of insulin. This is especially pertinent for rapid-acting insulin analogs that are more rapidly absorbed through skin and have shorter duration of action. These differences may be particularly relevant when patients are switched from multiple injection therapy or infusion with buffered regular insulin. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim therapy with subcutaneous injection may be required. (See PRECAUTIONS, Mixing of Insulins.)

PRECAUTIONS

General

Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated with the use of all insulins. Because of differences in the action of NovoLog and other insulins, care should be taken in patients in whom such potential side effects might be clinically relevant (e.g., patients who are fasting, have autonomic neuropathy, or are using potassium-lowering drugs or patients taking drugs sensitive to serum potassium level). Insulin stimulates potassium movement into the cells, possibly leading to hypokalemia that left untreated may cause respiratory paralysis, ventricular arrhythmia, and death. Since intravenously administered insulin has a rapid onset of action, increased attention to hypoglycemia and hypokalemia is necessary. Therefore, glucose and potassium levels must be monitored closely when NovoLog or any other insulin is administered intravenously. Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated with the use of all insulins. As with all insulin preparations, the time course of NovoLog 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. Insulin requirements may be altered during illness, emotional disturbances, or other stresses.

Hypoglycemia - As with all insulin preparations, hypoglycemic reactions may be associated with the administration of NovoLog. Rapid changes in serum glucose levels may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. 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.

Renal Impairment - As with other insulins, the dose requirements for NovoLog may be reduced in patients with renal impairment.

Hepatic Impairment - As with other insulins, the dose requirements for NovoLog may be reduced in patients with hepatic impairment.

Allergy - Local Allergy - As with other insulin therapy, patients may experience redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of NovoLog. 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 - Less common, but potentially more serious, is generalized allergy to insulin, which 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.

Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient.

In controlled clinical trials using injection therapy, allergic reactions were reported in 3 of 735 patients (0.4%) who received regular human insulin and 10 of 1394 patients (0.7%) who received NovoLog. During these and other trials, 3 of 2341 patients treated with NovoLog were discontinued due to allergic reactions.

Antibody Production - Increases in levels of anti-insulin antibodies that react with both human insulin and insulin aspart have been observed in patients treated with NovoLog. The number of patients treated with insulin aspart experiencing these increases is greater than the number among those treated with human regular insulin. Data from a 12-month controlled trial in patients with Type 1 diabetes suggest that the increase in these antibodies is transient. The differences in antibody levels between the human regular insulin and insulin aspart treatment groups observed at 3 and 6 months were no longer evident at 12 months. The clinical significance of these antibodies is not known. They do not appear to cause deterioration in HbA1c or to necessitate increases in insulin dose.

Pregnancy and Lactation - Female patients should be advised to tell their physician if they intend to become, or if they become pregnant. Information is not available on the use of NovoLog during pregnancy or lactation.

Usage in Pumps - NovoLog is recommended for use in pump systems suitable for insulin infusion as listed below.

Pumps: Disetronic H-TRON® series, MiniMed 500 series and other equivalent pumps.

Reservoirs and Infusion Sets: NovoLog is recommended for use in any reservoir and infusion sets that are compatible with insulin and the specific pump. In-vitro studies have shown that pump malfunction, loss of cresol, and insulin degradation may occur when NovoLog is maintained in a pump system for more than 48 hours. Reservoirs and infusion sets should be changed at least every 48 hours.

NovoLog in clinical use should not be exposed to temperatures greater than 37°C (98.6°F). **NovoLog should not be mixed with other insulins or with a diluent when it is used in the pump.** (See WARNINGS; PRECAUTIONS, Mixing of Insulins.)

Laboratory Tests

As with all insulin therapy, the therapeutic response to NovoLog should be monitored by periodic blood glucose tests. Periodic measurement of glycosylated hemoglobin is recommended for the monitoring of long-term glycemic control. When NovoLog is administered intravenously, glucose and potassium levels must be closely monitored to avoid potentially fatal hypoglycemia and hypokalemia.

Drug Interactions

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

Your trusted insulin analog for pumps—
FDA-approved since 2001.

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

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

• 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.

Mixing of Insulins

• A clinical study in healthy male volunteers (n=24) demonstrated that mixing NovoLog with NPH human insulin immediately before injection produced some attenuation in the peak concentration of NovoLog, but that the time to peak and the total bioavailability of NovoLog were not significantly affected. If NovoLog is mixed with NPH human insulin, NovoLog should be drawn into the syringe first. The injection should be made immediately after mixing. Because there are no data on the compatibility of NovoLog and crystalline zinc insulin preparations, NovoLog should not be mixed with these preparations.

• The effects of mixing NovoLog with insulins of animal source or insulin preparations produced by other manufacturers have not been studied (see WARNINGS).

• Mixtures should not be administered intravenously.

• **When used in external subcutaneous infusion pumps for insulin, NovoLog should not be mixed with any other insulins or diluent.**

Carcinogenicity, Mutagenicity, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of NovoLog. In 52-week studies, Sprague-Dawley rats were dosed subcutaneously with NovoLog at 10, 50, and 200 U/kg/day (approximately 2, 8, and 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area, respectively). At a dose of 200 U/kg/day, NovoLog increased the incidence of mammary gland tumors in females when compared to untreated controls. The incidence of mammary tumors for NovoLog was not significantly different than for regular human insulin. The relevance of these findings to humans is not known. NovoLog was not genotoxic in the following tests: Ames test, mouse lymphoma cell forward gene mutation test, human peripheral blood lymphocyte chromosome aberration test, in vivo micronucleus test in mice, and in vivo UDS test in rat liver hepatocytes. In fertility studies in male and female rats, at subcutaneous doses up to 200 U/kg/day (approximately 32 times the human subcutaneous dose, based on U/body surface area), no direct adverse effects on male and female fertility, or general reproductive performance of animals was observed.

Pregnancy - Teratogenic Effects - Pregnancy Category C

There are no adequate well-controlled clinical studies of the use of NovoLog in pregnant women. NovoLog should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in such patients.

Subcutaneous reproduction and teratology studies have been performed with NovoLog and regular human insulin in rats and rabbits. In these studies, NovoLog was given to female rats before mating, during mating, and throughout pregnancy, and to rabbits during organogenesis. The effects of NovoLog did not differ from those observed with subcutaneous regular human insulin. NovoLog, like human insulin, caused pre- and post-implantation losses and visceral/skeletal abnormalities in rats at a dose of 200 U/kg/day (approximately 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area) and in rabbits at a dose of 10 U/kg/day (approximately three times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area). The effects are probably secondary to maternal hypoglycemia at high doses. No significant effects were observed in rats at a dose of 50 U/kg/day and rabbits at a dose of 3 U/kg/day. These doses are approximately 8 times the human subcutaneous dose of 1.0 U/kg/day for rats and equal to the human subcutaneous dose of 1.0 U/kg/day for rabbits, based on U/body surface area.

Nursing Mothers

It is unknown whether insulin aspart is excreted in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when NovoLog is administered to a nursing mother.

Pediatric Use

A 24-week, parallel-group study of children and adolescents with Type 1 diabetes (n=283) age 6 to 18 years compared the following treatment regimens: NovoLog (n=187) or Novolin R (n=96). NPH insulin was administered as the basal insulin. NovoLog achieved glycemic control comparable to Novolin R, as measured by change in HbA1c. The incidence of hypoglycemia was similar for both treatment groups. NovoLog and regular human insulin have also been compared in children with Type 1 diabetes (n=26) age 2 to 6 years. As measured by end-of-treatment HbA1c and fructosamine, glycemic control with NovoLog was comparable to that obtained with regular human insulin. As observed in the 6 to 18 year old pediatric population, the rates of hypoglycemia were similar in both treatment groups.

Geriatric Use

Of the total number of patients (n=1375) treated with NovoLog in 3 human insulin-controlled clinical studies, 2.6% (n=36) were 65 years of age or over. Half of these patients had Type 1 diabetes (18/1285) and half had Type 2 (18/90) diabetes. The HbA1c response to NovoLog, as compared to human insulin, did not differ by age, particularly in patients with Type 2 diabetes. Additional studies in larger populations of patients 65 years of age or over are needed to permit conclusions regarding the safety of NovoLog in elderly compared to younger patients. Pharmacokinetic/pharmacodynamic studies to assess the effect of age on the onset of NovoLog action have not been performed.

ADVERSE REACTIONS

Clinical trials comparing NovoLog with regular human insulin did not demonstrate a difference in frequency of adverse events between the two treatments.

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

Body as Whole - Allergic reactions (see PRECAUTIONS, Allergy).

Skin and Appendages - Injection site reaction, lipodystrophy, pruritus, rash (see PRECAUTIONS, Allergy, Usage in Pumps).

Other - Hypoglycemia, hyperglycemia and ketosis (see WARNINGS and PRECAUTIONS). In controlled clinical trials, small, but persistent elevations in alkaline phosphatase result were observed in some patients treated with NovoLog. The clinical significance of this finding is unknown.

OVERDOSAGE

Excess insulin may cause hypoglycemia and hypokalemia, particularly during IV administration. 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. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

More detailed information is available on request.

Rx only

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