

## POLICY & PRACTICE

### Chronic Disease: \$1 Trillion a Year

Seven chronic diseases—cancer, diabetes, hypertension, stroke, heart disease, pulmonary conditions, and mental illness—have a total impact on the economy of \$1.3 trillion annually, including \$1.1 trillion in lost productivity, according to a study by the Milken Institute. That figure could be nearly \$6 trillion by midcentury, the report said. “By investing in good health, we can add billions of dollars in economic growth in the coming decades,” said Ross C. DeVol, the institute’s director of regional economics and principal author of the report. He noted that much of this cost was avoidable. “With moderate improvements in prevention and early intervention ... the savings to the economy would be enormous.” West Virginia, Tennessee, Arkansas, Kentucky, and Mississippi have the highest rates of chronic disease. Utah, Alaska, Colorado, New Mexico, and Arizona have the lowest.

### Senate Committee Knocks GSK Actions on Avandia

The Senate Finance Committee has issued a report criticizing GlaxoSmithKline for its alleged efforts to tone down one of the more prominent critics of its drug rosiglitazone (Avandia). The report referred to “what appears to be an orchestrated plan to stifle the opinion of Dr. John Buse,” the current president of the American Diabetes Association. The report looked back to 1999, when Dr. Buse raised the possibility that rosiglitazone could have the potential to increase cardiovascular events in those who took it. GlaxoSmithKline eventually had Dr. Buse sign a letter clarifying some of his earlier statements. The committee called the company’s behavior “less than stellar” and said that the public good “would have been better served” if Dr. Buse had been allowed to continue voicing his concerns. In a statement, the company said it disagreed with the committee’s findings and said that it did not require Dr. Buse to sign a legal document restricting his comments. Instead, the company said it was “trying to correct inaccuracies about data on Avandia in a continuing medical education presentation by Dr. Buse. ... Ultimately, GSK staff communicated their concerns to Dr. Buse and his supervisor. Dr. Buse clarified and corrected his statements, which the company appreciated.” The statement noted that “GSK understands that there is a fundamental difference between engaging in scientific debate to ensure the accuracy of public statements, and trying to inappropriately influence or silence a critic.... The company does not support or condone efforts to silence critics.”

### Heart Drugs Skewing Younger

More people aged 20-44 years are taking prescription medications for cardiac conditions—and their ranks are growing faster than those aged 45 or older who use the therapies, according to Medco Health Solutions. Extrapolating data from 2.5 million Medco drug benefit users, the company estimated that nationally 4.2 million patients aged 20-44 years took lipid-lowering drugs in 2006—a 68% increase from 2001—and 8.5 million took antihypertensives, a 21% rise from 2001. The rate of increase for new users of lipid-lowering drugs was 37%

higher for those younger than 45 years than for patients 45-64 years. “The bad news is that these conditions are showing up in patients at younger ages,” Medco chief medical officer Dr. Robert Epstein said in a statement.

### Low Health Literacy Is Costly

Researchers found that 87 million adults, or 36% of the adult U.S. population, have basic or below basic health literacy skills. Using data from the 2003 Department of Education National Assessment of Adult Health Literacy, they estimated that low

health literacy costs the U.S. economy between \$106 billion and \$236 billion a year. “Our findings suggest that low health literacy exacts enormous costs on both the health system and society,” lead author John A. Vernon, Ph.D., said in a statement. The report, “Low Health Literacy: Implications for National Health Policy,” was supported by a grant from Pfizer Inc.

### Medicare Out-of-Pocket Spending Rises

The percentage of income that Medicare beneficiaries spend on out-of-pocket health care costs is rising, according to a study published in the November/December issue of Health Affairs. The me-

dian amount of income that Medicare beneficiaries spent out of pocket was 12% in 1997, but rose to 16% in 2003. Study authors Patricia Neuman, Sc.D., of the Henry J. Kaiser Family Foundation, and colleagues noted that in 2003, the 25% of beneficiaries with the highest out-of-pocket expenses spent at least 30% of their income on health care, while the top 10% spent at least 58%. “Our findings suggest that giving elderly and disabled Medicare beneficiaries more ‘skin in the game’ could make health care less affordable and accessible for all but the highest-income beneficiaries,” the researchers said.

—Joyce Frieden

**References:** 1. Brange J, Vølund A. Insulin analogs with improved pharmacokinetic profiles. *Adv Drug Deliv Rev.* 1999;35(2-3):307-335. 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(5):583-588. 3. Korytkowski M, Bell D, Jacobsen C, Suwannasari R, for the FlexPen® Study Team. A multicenter, randomized, open-label, comparative, two-period crossover trial of preference, efficacy, and safety profiles of a prefilled, disposable pen and conventional vial/syringe for insulin injection in patients with type 1 or 2 diabetes mellitus. *Clin Ther.* 2003;25(11):2836-2848. 4. 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(4):531-540.

## NovoLog®

Insulin aspart (rDNA origin) injection

**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 lactation (see PREGNANCY-TERATOGENIC EFFECTS-PREGNANCY CATEGORY).

**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.

- 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 ex 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 B

All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. 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.

An open-label, randomized study compared the safety and efficacy of NovoLog versus human insulin in the treatment of pregnant women with Type 1 diabetes (322 exposed pregnancies (NovoLog: 157, human insulin: 165)). Two-thirds of the enrolled patients were already pregnant when they entered the study. Since only one-third of the patients enrolled before conception, the study was not large enough to evaluate the risk of congenital malformations. Mean HbA1c of ~6% was observed in both groups during pregnancy, and there was no significant difference in the incidence of maternal hypoglycemia.

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=1,375) 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 a 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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