CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020986Orig1s047

Trade Name: NOVOLOG®

Generic or Proper Name: Insulin aspart (rDNA origin) Injection

Sponsor: Novo Nordisk Inc.

Approval Date: 03/14/2008

Indication: NovoLog is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020986/S-047

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020986/S-047

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-986/S-047

Novo Nordisk, Inc.
Attention: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

SUPPLEMENT APPROVAL

Dear Dr. McElligott:

Please refer to your supplemental new drug application dated May 11, 2007, received May 14, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NovoLog (insulin aspart [rDNA origin] injection).

We acknowledge receipt of your submissions dated: August 8 and 29, October 10, and November 12, 2007, and January 16, February 15 and 28, and March 11, 12, 13, and 14, 2008.

This supplemental new drug application provides for the use of NovoLog for pediatric pump use.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert submitted March 14, 2008**,** text for the patient package insert submitted March 14, 2008, and Patient Instructions for Use: Vial, cartridge, and prefilled syringe submitted March 14, 2008.) Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 20-986/S-047**."

PEDIATRIC RESEARCH EQUITY ACT (PREA)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this supplemental application.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Package Insert
Patient Package Insert
Flexpen Instructions for Use Leaflet
PenFill Instructions for Use Leaflet
Vial Instructions for Use Leaflet

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mary Parks

3/14/2008 07:00:44 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020986/S-047

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NovoLog® safely and effectively. See full prescribing information for NovoLog.

NovoLog (insulin aspart [rDNA origin] injection) solution for subcutaneous use
Initial U.S. Approval: 2000

·····INDICATIONS AND USAGE·····

- NovoLog is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus (1.1)

·····DOSAGE AND ADMINISTRATION·····

- The dosage of NovoLog must be individualized.
- *Subcutaneous injection* NovoLog should generally be given immediately (within 5-10 minutes) prior to the start of a meal (2.2)
- *Use in pumps*: Change the NovoLog in the reservoir, the infusion set, and the infusion set insertion site at least every 48 hours. NovoLog should not be mixed with other insulins or with a diluent when it is used in the pump. (2.3)
- *Intravenous use*: NovoLog should be used at concentrations from 0.05 U/mL to 1.0 U/mL insulin aspart in infusion systems using polypropylene infusion bags. NovoLog has been shown to be stable in infusion fluids such as 0.9% sodium chloride. (2.4)

·····DOSAGE FORMS AND STRENGTHS·····

Each presentation contains 100 Units of insulin aspart per mL (U-100)

- 10 mL vials (3)
- 3 mL PenFill® cartridges for the 3 mL PenFill cartridge device (3)
- 3 mL NovoLog FlexPen Prefilled syringe (3)

·····CONTRAINDICATIONS·····

- Do not use during episodes of hypoglycemia (4)
- Do not use in patients with hypersensitivity to NovoLog or one of its excipients.

·····WARNINGS AND PRECAUTIONS·····

- Hypoglycemia is the most common adverse effect of insulin therapy. Glucose monitoring is recommended for all patients with diabetes. Any change of insulin dose should be made cautiously and only under medical supervision. (5.1, 5.2).
- Insulin, particularly when given intravenously or in settings of poor glycemic control, can cause hypokalemia. Use caution in patients predisposed to hypokalemia (5.3).
- Like all insulins, NovoLog requirements may be reduced in patients with renal impairment or hepatic impairment (5.4, 5.5)
- Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with insulin products, including NovoLog.(5.7)

·····ADVERSE REACTIONS·····

Adverse reactions observed with NovoLog include hypoglycemia, allergic reactions, local injection site reactions, lipodystrophy, rash and pruritus. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-800-727-6500 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

·····DRUG INTERACTIONS·····

- The following may increase the blood glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetic products, pramlintide, ACE inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, propoxyphene, salicylates, somatostatin analogs, sulfonamide antibiotics. (7)
- The following 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), atypical antipsychotics. (7)
- Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. (7)
- Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia. (7)
- The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic products such as beta-blockers, clonidine, guanethidine, and reserpine. (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: [3/2008]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of diabetes mellitus

NovoLog is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

NovoLog is an insulin analog with an earlier onset of action than regular human insulin. The dosage of NovoLog must be individualized. NovoLog given by subcutaneous injection should generally be used in regimens with an intermediate or long-acting insulin. [*see Warnings and Precautions (5), How Supplied/Storage and Handling (16.2)*]. The total daily insulin requirement may vary and is usually between 0.5 to 1.0 units/kg/day. When used in a meal-related subcutaneous injection treatment regimen, 50 to 70% of total insulin requirements may be provided by NovoLog and the remainder provided by an intermediate-acting or long-acting insulin. Because of NovoLog's comparatively rapid onset and short duration of glucose lowering activity, some patients may require more basal insulin and more total insulin to prevent pre-meal hyperglycemia when using NovoLog than when using human regular insulin.

Do not use NovoLog that is viscous (thickened) or cloudy; use only if it is clear and colorless. NovoLog should not be used after the printed expiration date.

2.2 Subcutaneous injection

NovoLog should be administered by subcutaneous injection in the abdominal region, buttocks, thigh, or upper arm. Because NovoLog has a more rapid onset and a shorter duration of activity than human regular insulin, it should be injected immediately (within 5-10 minutes) before a meal. Injection sites should be rotated within the same region to reduce the risk of lipodystrophy. As with all insulins, the duration of action of NovoLog will vary according to the dose, injection site, blood flow, temperature, and level of physical activity.

NovoLog may be diluted with Insulin Diluting Medium for NovoLog for subcutaneous injection. Diluting one part NovoLog to nine parts diluent will yield a concentration one-tenth that of NovoLog (equivalent to U-10). Diluting one part NovoLog to one part diluent will yield a concentration one-half that of NovoLog (equivalent to U-50).

2.3 Continuous subcutaneous insulin infusion (CSII) by external pump

NovoLog can also be infused subcutaneously by an external insulin pump [*see Warnings and Precautions (5.9, 5.10), How Supplied/Storage and Handling (16.2)*]. Diluted insulin should not be used in external insulin pumps. Because NovoLog has a more rapid onset and a shorter duration of activity than human regular insulin, pre-meal boluses of NovoLog should be infused immediately (within 5-10 minutes) before a meal. Infusion sites should be rotated within the same region to reduce the risk of lipodystrophy. The initial programming of the external insulin infusion pump should be based on the total daily insulin dose of the previous regimen. Although there is significant interpatient variability, approximately 50% of the total dose is usually given as meal-related boluses of NovoLog and the remainder is given as a basal infusion. **Change the**

NovoLog in the reservoir, the infusion sets and the infusion set insertion site at least every 48 hours.

2.4 Intravenous Use

NovoLog can be administered intravenously under medical supervision for glycemic control with close monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia [*see Warnings and Precautions (5.9), How Supplied/Storage and Handling (16.2)*]. For intravenous use, NovoLog should be used at concentrations from 0.05 U/mL to 1.0 U/mL insulin aspart in infusion systems using polypropylene infusion bags. NovoLog has been shown to be stable in infusion fluids such as 0.9% sodium chloride.

Inspect NovoLog for particulate matter and discoloration prior to parenteral administration.

3 DOSAGE FORMS AND STRENGTHS

NovoLog is available in the following package sizes: each presentation contains 100 units of insulin aspart per mL (U-100).

- 10 mL vials
- 3 mL PenFill cartridges for the 3mL PenFill cartridge delivery device (with or without the addition of a NovoPen® 3 PenMate®) with NovoFine® disposable needles
- 3 mL NovoLog FlexPen Prefilled Syringe

4 CONTRAINDICATIONS

NovoLog is contraindicated

- during episodes of hypoglycemia
- in patients with hypersensitivity to NovoLog or one of its excipients.

5 WARNINGS AND PRECAUTIONS

5.1 Administration

NovoLog has a more rapid onset of action and a shorter duration of activity than regular human insulin. An injection of NovoLog should immediately be followed by a meal within 5-10 minutes. Because of Novolog's short duration of action, a longer acting insulin should also be used in patients with type 1 diabetes and may also be needed in patients with type 2 diabetes. Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using external pump infusion therapy.

Any change of insulin dose should be made cautiously and only under medical supervision. Changing from one insulin product to another or changing the insulin strength may result in the need for a change in dosage. 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 many conditions, including the site of injection, local blood supply, temperature, and physical activity. Patients who change their level of physical activity or meal plan may require adjustment of insulin dosages. Insulin requirements may be altered during illness, emotional disturbances, or other stresses.

Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure.

5.2 Hypoglycemia

Hypoglycemia is the most common adverse effect of all insulin therapies, including NovoLog. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person and/or parenteral glucose infusion or glucagon administration has been observed in clinical trials with insulin, including trials with NovoLog.

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations [*see Clinical Pharmacology (12)*]. Other factors such as changes in food intake (e.g., amount of food or timing of meals), injection site, exercise, and concomitant medications may also alter the risk of hypoglycemia [*see Drug Interactions (7)*]. As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., patients who are fasting or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.

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 longstanding diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control [*see Drug Interactions (7)*]. These situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia. Intravenously administered insulin has a more rapid onset of action than subcutaneously administered insulin, requiring more close monitoring for hypoglycemia.

5.3 Hypokalemia

All insulin products, including NovoLog, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia that, if left untreated, may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations, and patients receiving intravenously administered insulin).

5.4 Renal Impairment

As with other insulins, the dose requirements for NovoLog may be reduced in patients with renal impairment [*see Clinical Pharmacology (12.3)*].

5.5 Hepatic Impairment

As with other insulins, the dose requirements for NovoLog may be reduced in patients with hepatic impairment [*see Clinical Pharmacology (12.3)*].

5.6 Hypersensitivity and Allergic Reactions

Local Reactions - As with other insulin therapy, patients may experience redness, swelling, or itching at the site of NovoLog injection. These 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. Localized reactions and generalized myalgias have been reported with injected metacresol, which is an excipient in NovoLog.

Systemic Reactions - Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with any insulin product, including NovoLog. Anaphylactic reactions with NovoLog have been reported post-approval. Generalized allergy to insulin may also cause whole body rash (including pruritus), dyspnea, wheezing, hypotension, tachycardia, or diaphoresis. In controlled clinical trials, allergic reactions were reported in 3 of 735 patients (0.4%) treated with regular human insulin and 10 of 1394 patients (0.7%) treated with NovoLog. In controlled and uncontrolled clinical trials, 3 of 2341 (0.1%) NovoLog-treated patients discontinued due to allergic reactions.

5.7 Antibody Production

Increases in anti-insulin antibody titers that react with both human insulin and insulin aspart have been observed in patients treated with NovoLog. Increases in anti-insulin antibodies are observed more frequently with NovoLog than with regular human insulin. Data from a 12-month controlled trial in patients with type 1 diabetes suggest that the increase in these antibodies is transient, and the differences in antibody levels between the regular human 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. These antibodies do not appear to cause deterioration in glycemic control or necessitate increases in insulin dose.

5.8 Mixing of Insulins

- Mixing NovoLog with NPH human insulin immediately before injection attenuates the peak concentration of NovoLog, without significantly affecting the time to peak concentration or total bioavailability of NovoLog. If NovoLog is mixed with NPH human insulin, NovoLog should be drawn into the syringe first, and the mixture should be injected immediately after mixing.
- The efficacy and safety of mixing NovoLog with insulin preparations produced by other manufacturers have not been studied.
- Insulin mixtures should not be administered intravenously.

5.9 Subcutaneous continuous insulin infusion by external pump

When used in an external subcutaneous insulin infusion pump, NovoLog should not be mixed with any other insulin or diluent. When using NovoLog in an external insulin pump, the NovoLog-specific information should be followed (e.g., in-use time, frequency of changing infusion sets) because NovoLog-specific information may differ from general pump manual instructions.

Pump or infusion set malfunctions or insulin degradation can lead to a rapid onset of hyperglycemia and ketosis 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 a shorter duration of action. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim therapy with subcutaneous injection may be required. [*see Dosage and Administration (2.3), Warnings and Precautions (5.9, 5.10), How Supplied/Storage and Handling (16.2), and Patient Counseling Information (17)*]

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

Pumps:

MiniMed 500 series and other equivalent pumps.

Reservoirs and infusion sets:

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

NovoLog should not be exposed to temperatures greater than 37°C (98.6°F). **NovoLog that will be used in a pump should not be mixed with other insulin or with a diluent.** [*see Dosage and Administration (2.3), Warnings and Precautions (5.9, 5.10) and How Supplied/Storage and Handling (16.2), Patient Counseling Information (17)*].

6 ADVERSE REACTIONS

Clinical Trial Experience

Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

- *Hypoglycemia*

  Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including NovoLog. [*see Warnings and Precautions (5)*]

- *Insulin initiation and glucose control intensification*

  Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

- *Lipodystrophy*

  Long-term use of insulin, including NovoLog, can cause lipodystrophy at the site of repeated insulin injections or infusion. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy.

- *Weight gain*

Weight gain can occur with some insulin therapies, including NovoLog, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

- *Peripheral Edema*

Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

- *Frequencies of adverse drug reactions*

The frequencies of adverse drug reactions during NovoLog clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

Table 1: Treatment-Emergent Adverse Events in Patients with Type 1 Diabetes Mellitus (Adverse events with frequency ≥ 5% and occurring more frequently with NovoLog compared to human regular insulin are listed)

	NovoLog + NPH N= 596		Human Regular Insulin + NPH N= 286	
Preferred Term	**N**	**(%)**	**N**	**(%)**
Hypoglycemia*	448	75%	205	72%
Headache	70	12%	28	10%
Injury accidental	65	11%	29	10%
Nausea	43	7%	13	5%
Diarrhea	28	5%	9	3%

*Hypoglycemia is defined as an episode of blood glucose concentration <45 mg/dL with or without symptoms. See Section 14 for the incidence of serious hypoglycemia in the individual clinical trials.

Table 2: Treatment-Emergent Adverse Events in Patients with Type 2 Diabetes Mellitus (except for hypoglycemia, adverse events with frequency ≥ 5% and occurring more frequently with NovoLog compared to human regular insulin are listed)

	NovoLog + NPH N= 91		Human Regular Insulin + NPH N= 91	
	N	**(%)**	**N**	**(%)**
Hypoglycemia*	25	27%	33	36%
Hyporeflexia	10	11%	6	7%
Onychomycosis	9	10%	5	5%
Sensory disturbance	8	9%	6	7%
Urinary tract infection	7	8%	6	7%
Chest pain	5	5%	3	3%
Headache	5	5%	3	3%
Skin disorder	5	5%	2	2%
Abdominal pain	5	5%	1	1%
Sinusitis	5	5%	1	1%

*Hypoglycemia is defined as an episode of blood glucose concentration <45 mg/dL,with or without symptoms. See Section 14 for the incidence of serious hypoglycemia in the individual clinical trials.

Postmarketing Data

The following additional adverse reactions have been identified during postapproval use of NovoLog. Because these adverse reactions are reported voluntarily from a population of

uncertain size, it is generally not possible to reliably estimate their frequency. Medication errors in which other insulins have been accidentally substituted for NovoLog have been identified during postapproval use. [*see Patient Counseling Information (17)*]

7 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, pramlintide, 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), atypical antipsychotics.
- 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.
- The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic products such as beta-blockers, clonidine, guanethidine, and reserpine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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 these patients. Therefore, female patients should be advised to tell their physician if they intend to become, or if they become pregnant while taking NovoLog

An open-label, randomized study compared the safety and efficacy of NovoLog (n=157) versus regular human insulin (n=165) in 322 pregnant women with type 1 diabetes. Two-thirds of the enrolled patients were already pregnant when they entered the study. Because only one-third of the patients enrolled before conception, the study was not large enough to evaluate the risk of congenital malformations. Both groups achieved a mean HbA_{1c} of ~ 6% 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 in 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.

8.3 Nursing Mothers

It is unknown whether insulin aspart is excreted in human milk. Use of NovoLog is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

8.4 Pediatric Use

NovoLog is approved for use in children for subcutaneous daily injections and for subcutaneous continuous infusion by external insulin pump. Please see *Section 14* ***CLINICAL STUDIES*** for summaries of clinical studies.

8.5 Geriatric Use

Of the total number of patients (n= 1,375) treated with NovoLog in 3 controlled clinical studies, 2.6% (n=36) were 65 years of age or over. One-half of these patients had type 1 diabetes (18/1285) and the other half had type 2 diabetes (18/90) .The HbA_{1c} 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.

10 OVERDOSAGE

Excess insulin administration may cause hypoglycemia and, particularly when given intravenously, hypokalemia. 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.

11 DESCRIPTION

NovoLog (insulin aspart [rDNA origin] injection) is a rapid-acting human insulin analog used to lower blood glucose. NovoLog is homologous with regular human insulin with the exception of a single substitution of the amino acid proline by aspartic acid in position B28, and is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae* (baker's yeast). Insulin aspart has the empirical formula $C_{256}H_{381}N_{65}0_{79}S_6$ and a molecular weight of 5825.8.

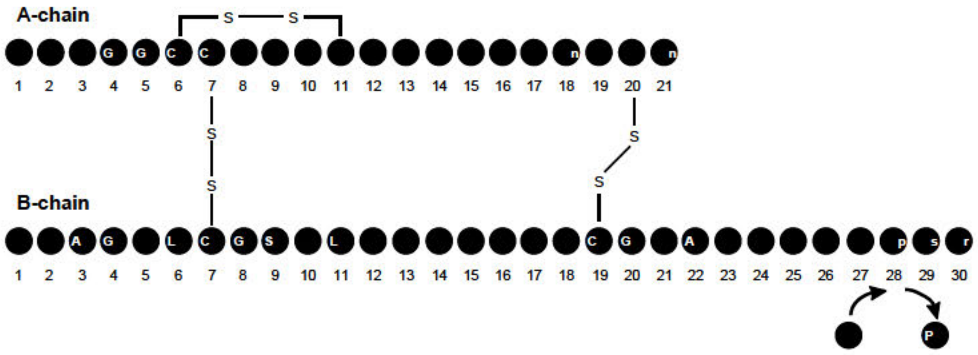


Figure 1. Structural formula of insulin aspart.

NovoLog is a sterile, aqueous, clear, and colorless solution, that contains insulin aspart 100 Units/mL, glycerin 16 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 19.6 mcg/mL, disodium hydrogen phosphate dihydrate 1.25 mg/mL, and sodium chloride 0.58 mg/mL. NovoLog has a pH of 7.2-7.6. Hydrochloric acid 10% and/or sodium hydroxide 10% may be added to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The primary activity of NovoLog is the regulation of glucose metabolism. Insulins, including NovoLog, bind to the insulin receptors on muscle and fat cells and lower blood glucose by facilitating the cellular uptake of glucose and simultaneously inhibiting the output of glucose from the liver.

12.2 Pharmacodynamics

Studies in normal volunteers and patients with diabetes demonstrated that subcutaneous administration of NovoLog has a more rapid onset of action than regular human insulin.

In a study in patients with type 1 diabetes (n=22), the maximum glucose-lowering effect of NovoLog occurred between 1 and 3 hours after subcutaneous injection (see Figure 2). The duration of action for NovoLog is 3 to 5 hours. The time course of action of insulin and insulin analogs such as NovoLog may vary considerably in different individuals or within the same individual. The parameters of NovoLog activity (time of onset, peak time and duration) as designated in Figure 2 should be considered only as general guidelines. The rate of insulin absorption and onset of activity is affected by the site of injection, exercise, and other variables [*see Warnings and Precautions (5.1)*].

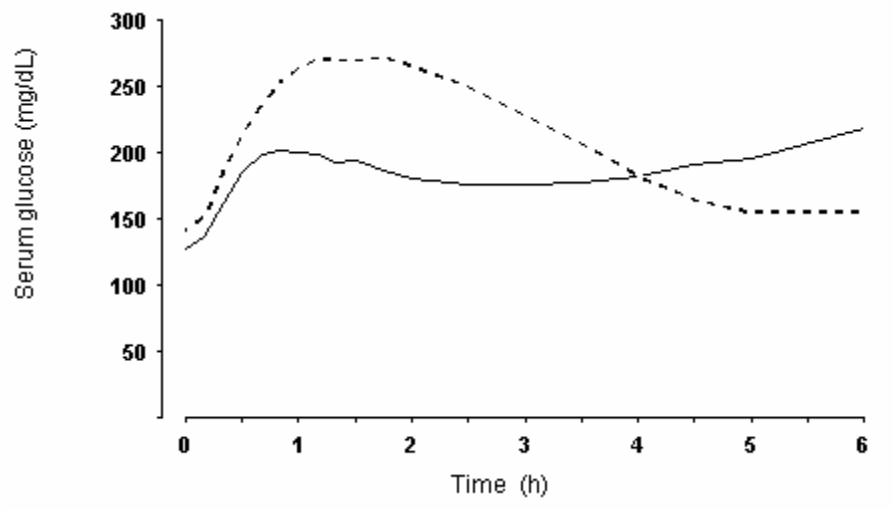


Figure 2. Serial mean serum glucose collected up to 6 hours following a single pre-meal dose of NovoLog (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with type 1 diabetes.

A double-blind, randomized, two-way cross-over study in 16 patients with type 1 diabetes demonstrated that intravenous infusion of NovoLog resulted in a blood glucose profile that was similar to that after intravenous infusion with regular human insulin. NovoLog or human insulin was infused until the patient's blood glucose decreased to 36 mg/dL, or until the patient demonstrated signs of hypoglycemia (rise in heart rate and onset of sweating), defined as the time of autonomic reaction (R) (see Figure 3).

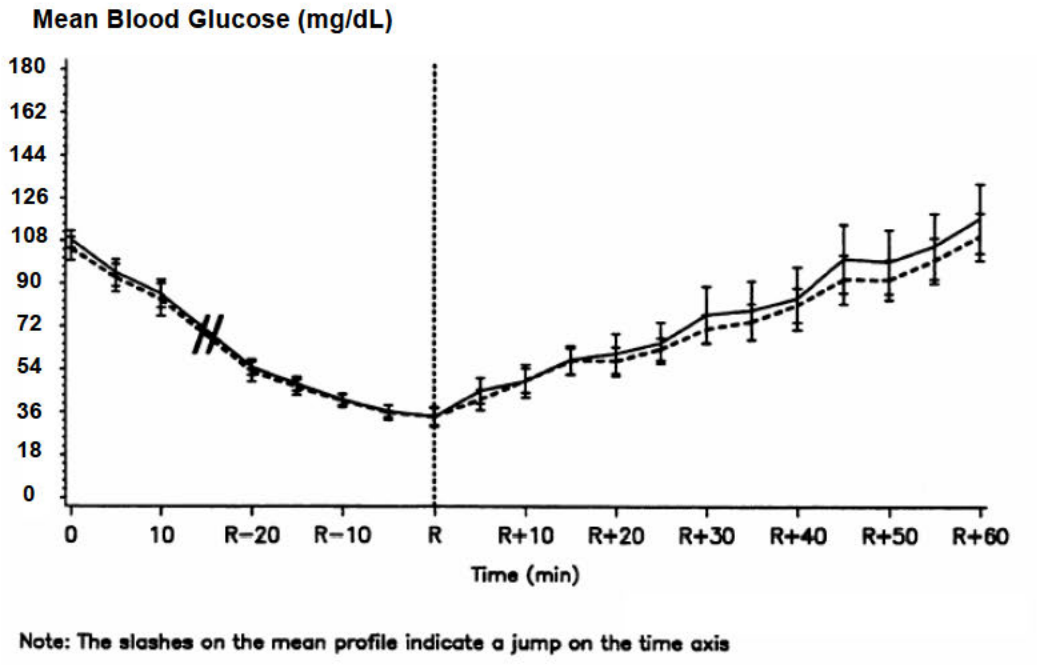


Figure 3. Mean blood glucose profiles following intravenous infusion of NovoLog (hatched curve) and regular human insulin (solid curve) in 16 patients with type 1 diabetes. R represents the time of autonomic reaction.

12.3 Pharmacokinetics

The single substitution of the amino acid proline with aspartic acid at position B28 in NovoLog reduces the molecule's tendency to form hexamers as observed with regular human insulin. NovoLog is, therefore, more rapidly absorbed after subcutaneous injection compared to regular human insulin.

In a randomized, double-blind, crossover study 17 healthy Caucasian male subjects between 18 and 40 years of age received an intravenous infusion of either NovoLog or regular human insulin at 1.5 mU/kg/min for 120 minutes. The mean insulin clearance was similar for the two groups with mean values of 1.2 l/h/kg for the NovoLog group and 1.2 l/h/kg for the regular human insulin group.

Bioavailability and Absorption - NovoLog has a faster absorption, a faster onset of action, and a shorter duration of action than regular human insulin after subcutaneous injection (see Figure 2 and Figure 4). The relative bioavailability of NovoLog compared to regular human insulin indicates that the two insulins are absorbed to a similar extent.

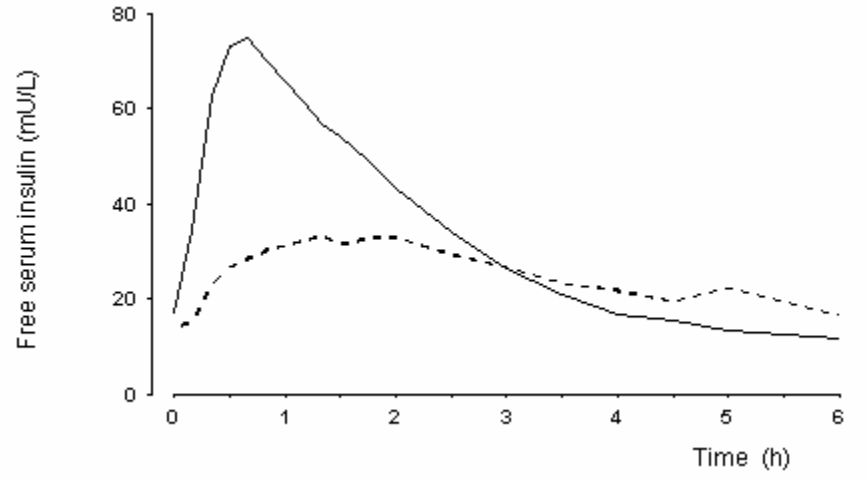


Figure 4. Serial mean serum free insulin concentration collected up to 6 hours following a single pre-meal dose of NovoLog (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with type 1 diabetes.

In studies in healthy volunteers (total n=l07) and patients with type 1 diabetes (total n=40), NovoLog consistently reached peak serum concentrations approximately twice as fast as regular human insulin. The median time to maximum concentration in these trials was 40 to 50 minutes for NovoLog versus 80 to 120 minutes for regular human insulin. In a clinical trial in patients with type 1 diabetes, NovoLog and regular human insulin, both administered subcutaneously at a dose of 0.15 U/kg body weight, reached mean maximum concentrations of 82 and 36 mU/L, respectively. Pharmacokinetic/pharmacodynamic characteristics of insulin aspart have not been established in patients with type 2 diabetes.

The intra-individual variability in time to maximum serum insulin concentration for healthy male volunteers was significantly less for NovoLog than for regular human insulin. The clinical significance of this observation has not been established.

In a clinical study in healthy non-obese subjects, the pharmacokinetic differences between NovoLog and regular human insulin described above, were observed independent of the site of injection (abdomen, thigh, or upper arm).

Distribution and Elimination - NovoLog has low binding to plasma proteins (<10%), similar to that seen with regular human insulin. After subcutaneous administration in normal male volunteers (n=24), NovoLog was more rapidly eliminated than regular human insulin with an average apparent half-life of 81 minutes compared to 141 minutes for regular human insulin.

Specific Populations

Children and Adolescents - The pharmacokinetic and pharmacodynamic properties of NovoLog and regular human insulin were evaluated in a single dose study in 18 children (6-12 years, n=9) and adolescents (13-17 years [Tanner grade $\geq$ 2], n=9) with type 1 diabetes. The relative differences in pharmacokinetics and pharmacodynamics in children and adolescents with type 1 diabetes between NovoLog and regular human insulin were similar to those in healthy adult subjects and adults with type 1 diabetes.

Gender - In healthy volunteers, no difference in insulin aspart levels was seen between men and women when body weight differences were taken into account. There was no significant difference in efficacy noted (as assessed by HbA_{1c}) between genders in a trial in patients with type 1 diabetes.

Obesity - A single subcutaneous dose of 0.1 U/kg NovoLog was administered in a study of 23 patients with type 1 diabetes and a wide range of body mass index (BMI, 22-39 kg/m^2). The pharmacokinetic parameters, AUC and C_{max}, of NovoLog were generally unaffected by BMI in the different groups – BMI 19-23 kg/m^2 (N=4); BMI 23-27 kg/m^2 (N=7); BMI 27-32 kg/m^2 (N=6) and BMI >32 kg/m^2 (N=6). Clearance of NovoLog was reduced by 28% in patients with BMI >32 kg/m^2 compared to patients with BMI <23 kg/m^2.

Renal Impairment - Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. A single subcutaneous dose of 0.08 U/kg NovoLog was administered in a study to subjects with either normal (N=6) creatinine clearance (CLcr) (> 80 ml/min) or mild (N=7; CLcr = 50-80 ml/min), moderate (N=3; CLcr = 30-50 ml/min) or severe (but not requiring hemodialysis) (N=2; CLcr = <30 ml/min) renal impairment. In this small study, there was no apparent effect of creatinine clearance values on AUC and C_{max} of NovoLog. Careful glucose monitoring and dose adjustments of insulin, including NovoLog, may be necessary in patients with renal dysfunction [*see Warnings and Precautions (5.4)*].

Hepatic Impairment - Some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. A single subcutaneous dose of 0.06 U/kg NovoLog was administered in an open-label, single-dose study of 24 subjects (N=6/group) with different degree of hepatic impairment (mild, moderate and severe) having Child-Pugh Scores ranging from 0 (healthy volunteers) to 12 (severe hepatic impairment). In this small study, there was no correlation between the degree of hepatic failure and any NovoLog pharmacokinetic parameter. Careful glucose monitoring and dose adjustments of insulin, including NovoLog, may be necessary in patients with hepatic dysfunction [*see Warnings and Precautions (5.5)*].

The effect of age, ethnic origin, pregnancy and smoking on the pharmacokinetics and pharmacodynamics of NovoLog has not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, 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.

13.2 Animal Toxicology and/or pharmacology

In standard biological assays in mice and rabbits, one unit of NovoLog has the same glucose-lowering effect as one unit of regular human insulin. In humans, the effect of NovoLog is more rapid in onset and of shorter duration, compared to regular human insulin, due to its faster absorption after subcutaneous injection (see *Section 12* CLINICAL PHARMACOLOGY Figure 2 and Figure 4).

14 CLINICAL STUDIES

14.1 Subcutaneous Daily Injections

Two six-month, open-label, active-controlled studies were conducted to compare the safety and efficacy of NovoLog to Novolin R in adult patients with type 1 diabetes. Because the two study designs and results were similar, data are shown for only one study (see Table 3). NovoLog was administered by subcutaneous injection immediately prior to meals and regular human insulin was administered by subcutaneous injection 30 minutes before meals. NPH insulin was administered as the basal insulin in either single or divided daily doses. Changes in HbA_{1c} and the incidence rates of severe hypoglycemia (as determined from the number of events requiring intervention from a third party) were comparable for the two treatment regimens in this study (Table 3) as well as in the other clinical studies that are cited in this section. Diabetic ketoacidosis was not reported in any of the adult studies in either treatment group.

Table 3. Subcutaneous NovoLog Administration in Type 1 Diabetes (24 weeks; n=882)

	NovoLog + NPH	Novolin R + NPH
N	596	286
Baseline HbA_{1c} (%)*	7.9 ±1.1	8.0 ± 1.2
Change from Baseline HbA_{1c} (%)	-0.1 ± 0.8	0.0 ± 0.8
Treatment Difference in HbA_{1c} ,Mean (95% confidence interval)	-0.2 (-0.3, -0.1)	
Baseline insulin dose (IU/kg/24 hours)*	0.7 ± 0.2	0.7 ± 0.2
End-of-Study insulin dose (IU/kg/24 hours)*	0.7 ± 0.2	0.7 ± 0.2
Patients with severe hypoglycemia (n, %)**	104 (17%)	54 (19%)
Baseline body weight (kg)*	75.3 ± 14.5	75.9 ± 13.1
Weight Change from baseline (kg)*	0.5 ± 3.3	0.9 ± 2.9

*Values are Mean ± SD

**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

A 24-week, parallel-group study of children and adolescents with type 1 diabetes (n = 283) aged 6 to 18 years compared two subcutaneous multiple-dose 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 HbA_{1c} (Table 4) and both treatment groups had a comparable incidence of hypoglycemia. Subcutaneous administration of NovoLog and regular human insulin have also been compared in children with type 1 diabetes (n=26) aged 2 to 6 years with similar effects on HbA_{1c} and hypoglycemia.

Table 4. Pediatric Subcutaneous Administration of NovoLog in Type 1 Diabetes (24 weeks; n=283)

	NovoLog + NPH	Novolin R + NPH
N	187	96
Baseline HbA_{1c} (%)*	8.3 ± 1.2	8.3 ± 1.3
Change from Baseline HbA_{1c} (%)	0.1± 1.0	0.1± 1.1
Treatment Difference in $HbA_{1c,}$ Mean (95% confidence interval)	0.1 (-0.5, 0.1)	
Baseline insulin dose (IU/kg/24 hours)*	0.4 ± 0.2	0.6 ± 0.2
End-of-Study insulin dose (IU/kg/24 hours)*	0.4 ± 0.2	0.7 ± 0.2
Patients with severe hypoglycemia (n, %)**	11 (6%)	9 (9%)
Diabetic ketoacidosis (n, %)	10 (5%)	2 (2%)
Baseline body weight (kg)*	50.6 ± 19.6	48.7 ± 15.8
Weight Change from baseline (kg)*	2.7 ± 3.5	2.4 ± 2.6

*Values are Mean ± SD
**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

One six-month, open-label, active-controlled study was conducted to compare the safety and efficacy of NovoLog to Novolin R in patients with type 2 diabetes (Table 5). NovoLog was administered by subcutaneous injection immediately prior to meals and regular human insulin was administered by subcutaneous injection 30 minutes before meals. NPH insulin was administered as the basal insulin in either single or divided daily doses. Changes in HbA_{lc} and the rates of severe hypoglycemia (as determined from the number of events requiring intervention from a third party) were comparable for the two treatment regimens.

Table 5. Subcutaneous NovoLog Administration in Type 2 Diabetes (6 months; n=176)

	NovoLog + NPH	Novolin R + NPH
N	90	86
Baseline HbA_{1c} (%)*	8.1 ± 1.2	7.8 ± 1.1
Change from Baseline HbA_{1c} (%)	-0.3 ± 1.0	-0.1 ± 0.8
Treatment Difference in $HbA_{1c,}$ Mean (95% confidence interval)	- 0.1 (-0.4, -0.1)	
Baseline insulin dose (IU/kg/24 hours)*	0.6 ± 0.3	0.6 ± 0.3
End-of-Study insulin dose (IU/kg/24 hours)*	0.7 ± 0.3	0.7 ± 0.3
Patients with severe hypoglycemia (n, %)**	9 (10%)	5 (8%)
Baseline body weight (kg)*	88.4 ± 13.3	85.8 ± 14.8
Weight Change from baseline (kg)*	1.2 ± 3.0	0.4 ± 3.1

*Values are Mean ± SD
**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

14.2 Continuous subcutaneous insulin infusion (CSII) by external pump

Two open-label, parallel design studies (6 weeks [n=29] and 16 weeks [n=118]) compared NovoLog to buffered regular human insulin (Velosulin) in adults with type 1 diabetes receiving a subcutaneous infusion with an external insulin pump. The two treatment regimens had comparable changes in HbA_{1c} and rates of severe hypoglycemia.

Table 6. Adult Insulin Pump Study in Type 1 Diabetes (16 weeks; n=118)

	NovoLog	Buffered human insulin
N	59	59
Baseline HbA_{1c} (%)*	7.3 ± 0.7	7.5 ± 0.8
Change from Baseline HbA_{1c} (%)	0.0 ± 0.5	0.2 ± 0.6
Treatment Difference in $HbA_{1c,}$ Mean (95% confidence interval)	0.3 (-0.1, 0.4)	
Baseline insulin dose (IU/kg/24 hours)*	0.7 ± 0.8	0.6 ± 0.2
End-of-Study insulin dose (IU/kg/24 hours)*	0.7 ± 0.7	0.6 ± 0.2
Patients with severe hypoglycemia (n, %)**	1 (2%)	2 (3%)
Baseline body weight (kg)*	77.4 ± 16.1	74.8 ± 13.8
Weight Change from baseline (kg)*	0.1 ± 3.5	-0.0 ± 1.7

*Values are Mean ± SD

**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

A randomized, 16-week, open-label, parallel design study of children and adolescents with type 1 diabetes (n=298) aged 4-18 years compared two subcutaneous infusion regimens administered via an external insulin pump: NovoLog (n=198) or insulin lispro (n=100). These two treatments resulted in comparable changes from baseline in HbA_{1c} and comparable rates of hypoglycemia after 16 weeks of treatment (see Table 7).

Table 7. Pediatric Insulin Pump Study in Type 1 Diabetes (16 weeks; n=298)

	NovoLog	Lispro
N	198	100
Baseline HbA_{1c} (%)*	8.0 ± 0.9	8.2 ± 0.8
Change from Baseline HbA_{1c} (%)	-0.1 ± 0.8	-0.1 ± 0.7
Treatment Difference in $HbA_{1c,}$ Mean (95% confidence interval)	-0.1 (-0.3, 0.1)	
Baseline insulin dose (IU/kg/24 hours)*	0.9 ± 0.3	0.9 ± 0.3
End-of-Study insulin dose (IU/kg/24 hours)*	0.9 ± 0.2	0.9 ± 0.2
Patients with severe hypoglycemia (n, %)**	19 (10%)	8 (8%)
Diabetic ketoacidosis (n, %)	1 (0.5%)	0 (0)
Baseline body weight (kg)*	54.1 ± 19.7	55.5 ± 19.0
Weight Change from baseline (kg)*	1.8 ± 2.1	1.6 ± 2.1

*Values are Mean ± SD

**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

An open-label, 16-week parallel design trial compared pre-prandial NovoLog injection in conjunction with NPH injections to NovoLog administered by continuous subcutaneous infusion in 127 adults with type 2 diabetes. The two treatment groups had similar reductions in HbA_{1c} and rates of severe hypoglycemia (Table 8). [*see Indications and Usage (1), Dosage and Administration (2), Warnings and Precautions (5) and How Supplied/Storage and Handling (16.2)*]

Table 8. Pump Therapy in Type 2 Diabetes (16 weeks; n=127)

	NovoLog pump	NovoLog + NPH
N	66	61
Baseline HbA_{1c} (%)*	8.2 ± 1.4	8.0 ± 1.1
Change from Baseline HbA_{1c} (%)	-0.6 ± 1.1	-0.5 ± 0.9
Treatment Difference in $HbA_{1c,}$ Mean (95% confidence interval)	0.1 (0.4, 0.3)	
Baseline insulin dose (IU/kg/24 hours)*	0.7 ± 0.3	0.8 ± 0.5
End-of-Study insulin dose (IU/kg/24 hours)*	0.9 ± 0.4	0.9 ± 0.5
Baseline body weight (kg)*	96.4 ± 17.0	96.9 ± 17.9
Weight Change from baseline (kg)*	1.7 ± 3.7	0.7 ± 4.1

*Values are Mean ± SD

14.3 Intravenous Administration of NovoLog

See *Section 12.2* CLINICAL PHARMACOLOGY/Pharmacodynamics.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How supplied

NovoLog is available in the following package sizes: each presentation containing 100 Units of insulin aspart per mL (U-100).

10 mL vials	NDC 0169-7501-11
3 mL PenFill cartridges*	NDC 0169-3303-12
3 mL NovoLog FlexPen Prefilled syringe	NDC 0169-6339-10

*NovoLog PenFill cartridges are designed for use with Novo Nordisk 3 mL PenFill cartridge compatible insulin delivery devices (with or without the addition of a NovoPen 3 PenMate) with NovoFine disposable needles.

16.2 Recommended Storage

Unused NovoLog should be stored in a refrigerator between 2° and 8°C (36° to 46°F). Do not store in the freezer or directly adjacent to the refrigerator cooling element. **Do not freeze NovoLog and do not use NovoLog if it has been frozen.** NovoLog should not be drawn into a syringe and stored for later use.

Vials: After initial use a vial may be kept at temperatures below 30°C (86°F) for up to 28 days, but should not be exposed to excessive heat or sunlight. Opened vials may be refrigerated.

Unpunctured vials can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused vials in the carton so they will stay clean and protected from light.

PenFill cartridges or NovoLog FlexPen Prefilled Syringes:

Once a cartridge or a NovoLog FlexPen Prefilled syringe is punctured, it should be kept at temperatures below 30°C (86°F) for up to 28 days, but should not be exposed to excessive heat or sunlight. Cartridges or NovoLog FlexPen Prefilled syringes in use must NOT be stored in the refrigerator. Keep all PenFill® cartridges and disposable NovoLog FlexPen Prefilled syringes away from direct heat and sunlight. Unpunctured PenFill cartridges and NovoLog FlexPen Prefilled syringes can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused PenFill cartridges and NovoLog FlexPen Prefilled syringes in the carton so they will stay clean and protected from light.

Always remove the needle after each injection and store the 3 mL PenFill cartridge delivery device or NovoLog FlexPen Prefilled Syringe without a needle attached. This prevents contamination and/or infection, or leakage of insulin, and will ensure accurate dosing. Always use a new needle for each injection to prevent contamination.

Pump:

NovoLog in the pump reservoir should be discarded after at least every 48 hours of use or after exposure to temperatures that exceed 37°C (98.6°F).

Summary of Storage Conditions:

The storage conditions are summarized in the following table:

Table 9. Storage conditions for vial, PenFill cartridges and NovoLog FlexPen Prefilled syringe

NovoLog presentation	**Not in-use (unopened)** Room Temperature (below 30°C)	**Not in-use** (unopened) Refrigerated	**In-use (opened)** Room Temperature (below 30°C)
10 mL vial	28 days	Until expiration date	28 days (refrigerated/room temperature)
3 mL PenFill cartridges	28 days	Until expiration date	28 days (Do not refrigerate)
3 mL NovoLog FlexPen Prefilled syringe	28 days	Until expiration date	28 days (Do not refrigerate)

Storage of Diluted NovoLog

NovoLog diluted with Insulin Diluting Medium for NovoLog to a concentration equivalent to U-10 or equivalent to U-50 may remain in patient use at temperatures below 30°C (86°F) for 28 days.

Storage of NovoLog in Infusion Fluids

Infusion bags prepared as indicated under *Dosage and Administration (2)* are stable at room temperature for 24 hours. Some insulin will be initially adsorbed to the material of the infusion bag.

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling *(17.3)*]

17.1 Physician Instructions

Maintenance of normal or near-normal glucose control is a treatment goal in diabetes mellitus and has been associated with a reduction in diabetic complications. Patients should be informed about potential risks and benefits of NovoLog therapy including the possible adverse reactions. Patients should also 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 dose, instruction in the use of injection or subcutaneous infusion devices, and proper storage of insulin. Patients should be informed that frequent, patient-performed blood glucose measurements are needed to achieve optimal glycemic control and avoid both hyper- and hypoglycemia.

The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia should be advised to use caution when driving or operating machinery.

Accidental substitutions between NovoLog and other insulin products have been reported. Patients should be instructed to always carefully check that they are administering the appropriate insulin to avoid medication errors between NovoLog and any other insulin. **The written prescription for NovoLog should be written clearly, to avoid confusion with other insulin products, for example, NovoLog Mix 70/30.**

17.2 Patients using pumps

Patients using external pump infusion therapy should be trained in intensive insulin therapy with multiple injections and in the function of their pump and pump accessories.

Pumps:

NovoLog is recommended for use in 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. Please see recommended reservoir and infusion sets in the pump manual.

To avoid insulin degradation, infusion set occlusion, and loss of the preservative (metacresol), reservoirs, infusion sets, and injection site should be changed at least every 48 hours.

Insulin exposed to temperatures higher than 37°C (98.6°F) should be discarded. The temperature of the insulin may exceed ambient temperature when the pump housing, cover, tubing, or sport case is exposed to sunlight or radiant heat. Infusion sites that are erythematous, pruritic, or thickened should be reported to medical personnel, and a new site selected because continued infusion may increase the skin reaction and/or alter the absorption of NovoLog. 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 are particularly relevant when patients are switched from infused buffered regular insulin or multiple injection therapy. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Problems include pump malfunction, infusion set occlusion, leakage, disconnection or kinking, and degraded insulin. Less commonly, hypoglycemia from pump malfunction may occur. If these problems cannot be promptly corrected, patients should resume therapy with subcutaneous insulin injection and contact their physician. [*see Dosage and Administration (2), Warnings and Precautions (5) and How Supplied/Storage and Handling (16.2)*]

17.3 FDA Approved Patient Labeling

Rx only

Date of Issue: March 14, 2008

Version 14

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

Manufactured For Novo Nordisk Inc., Princeton, New Jersey 08540

www.novonordisk-us.com

Patient Information

NovoLog® (NO-voe-log)

(insulin aspart [rDNA origin] Injection)

Important:
Know your insulin. Do not change the type of insulin you use unless told to do so by your health care provider. The amount of insulin you take as well as the best time for you to take your insulin may need to change if you take a different type of insulin.

Make sure you know the type and strength of insulin prescribed for you.

Read the Patient Information that comes with NovoLog before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your health care provider about your diabetes or your treatment. Make sure you know how to manage your diabetes. Ask your healthcare provider if you have any questions about managing your diabetes.

What is NovoLog?

NovoLog is a man-made insulin that is used to control high blood sugar in adults and children with diabetes mellitus.

Who should not use NovoLog?

Do not take NovoLog if:

- Your blood sugar is too low (hypoglycemia)
- You are allergic to anything in NovoLog. See the end of this leaflet for a complete list of ingredients in NovoLog. Check with your healthcare provider if you are not sure.

Tell your health care provider:

- **about all of your medical conditions.** Medical conditions can affect your insulin needs and your dose of NovoLog.
- **if you are pregnant or breastfeeding**, You and your healthcare provider should talk about the best way to manage your diabetes while you are pregnant or breastfeeding. NovoLog has not been studied in nursing women.
- **about all medicines you take,** including prescriptions and non-prescription medicines, vitamins and herbal supplements. Your NovoLog dose may change if you take other medicines.

Know the medicines you take. Keep a list of your medicines with you to show your healthcare providers when you get a new medicine.

How should I take NovoLog?
Only use NovoLog if it appears clear and colorless. There may be air bubbles. This is normal. If it looks cloudy, thickened, or colored, or if it contains solid particles do not use it and call Novo Nordisk at 1-800-727-6500.

NovoLog comes in:

- 10 mL vials (small bottles) for use with syringe
- 3 mL PenFill® cartridges for use with the Novo Nordisk 3 mL PenFill cartridge compatible insulin delivery devices and NovoFine® disposable needles. The cartridge delivery device can be used with a NovoPen® 3 PenMate®
- 3 mL NovoLog FlexPen®

Read the instructions for use that come with your NovoLog product. Talk to your healthcare provider if you have any questions. Your healthcare provider should show you how to inject NovoLog before you start taking it.

- **Take NovoLog exactly as prescribed.** You should eat a meal within 5 to 10 minutes after using NovoLog to avoid low blood sugar.
- **NovoLog is a fast-acting insulin.** The effects of NovoLog start working 10 to 20 minutes after injection or bolus pump infusion.
- **Do not inject NovoLog if you do not plan to eat right after your injection or bolus pump infusion.**
- The greatest blood sugar lowering effect is between 1 and 3 hours after the injection or infusion. This blood sugar lowering lasts for 3 to 5 hours.
- **While using NovoLog you may have to change** your total dose of insulin, your dose of longer-acting insulin, or the number of injections of longer-acting insulin you use. Pump users given NovoLog may need to change the amount of total insulin given as a basal infusion.
- **Do not mix NovoLog:**
    - with any other insulins when used in a pump
    - with any insulins other than NPH when used with injections by syringe

  If your doctor recommends diluting NovoLog, follow your doctor's instructions exactly so that you know:

  - How to make NovoLog more dilute (that is, a smaller number of units of NovoLog for a given amount of liquid) and
  - How to use this more dilute form of NovoLog. **Do not use dilute insulin in a pump.**

- **Inject NovoLog into the skin of your stomach area, upper arms, buttocks or upper legs.** NovoLog may affect your blood sugar levels sooner if you inject it into the skin of your stomach area. **Never inject NovoLog into a vein or into a muscle.**
- **Change (rotate) your injection site within the chosen area (for example, stomach or upper arm) with each dose. Do not inject into the exact same spot for each injection.**
- **If you take too much NovoLog**, **your blood sugar may fall low (hypoglycemia).** You can treat mild low blood sugar (hypoglycemia) by drinking or eating something sugary right away (fruit juice, sugar candies, or glucose tablets). It is important to treat low blood sugar (hypoglycemia) right away because it could get worse and you could pass out (become unconscious). If you pass out you will need help from another person or emergency medical services right away, and will need treatment with a glucagon injection or treatment at a hospital. See "What are the possible side effects of NovoLog?" for more information on low blood sugar (hypoglycemia).
- **If you forget to take your dose of NovoLog, your blood sugar may go too high (hyperglycemia).** If high blood sugar (hyperglycemia) is not treated it can lead to serious problems, like loss of consciousness (passing out), coma or even death. Follow your healthcare provider's instructions for treating high blood sugar. Know your symptoms of high blood sugar which may include:
  - increased thirst
  - frequent urination
  - drowsiness
  - loss of appetite
  - a hard time breathing
  - fruity smell on the breath
  - high amounts of sugar and ketones in your urine
  - nausea, vomiting (throwing up) or stomach pain
- **Check your blood sugar levels.** Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.

Your insulin dosage may need to change because of:

- illness
- stress
- other medicines you take
- change in diet
- change in physical activity or exercise

What should I avoid while using NovoLog?

- **Alcohol.** Alcohol, including beer and wine, may affect your blood sugar when you take NovoLog®.

- **Driving and operating machinery.** You may have difficulty concentrating or reacting if you have low blood sugar (hypoglycemia). Be careful when you drive a car or operate machinery. Ask your healthcare provider if it is alright to drive if you often have:
    - low blood sugar
    - decreased or no warning signs of low blood sugar

What are the possible side effects of NovoLog?

- **low blood sugar (hypoglycemia).** Symptoms of low blood sugar may include:

    - sweating
    - dizziness or lightheadedness
    - shakiness
    - hunger
    - fast heart beat
    - tingling of lips and tongue
    - trouble concentrating or confusion
    - blurred vision
    - slurred speech
    - anxiety, irritability or mood changes
    - headache

    Severe low blood sugar can cause unconsciousness (passing out), seizures, and death. Know your symptoms of low blood sugar. Follow your healthcare provider's instructions for treating low blood sugar. Talk to your healthcare provider if low blood sugar is a problem for you.

- **Serious allergic reaction (whole body reaction). Get medical help right away, if you develop** a rash over your whole body, have trouble breathing, a fast heartbeat, or sweating.
- **Reactions at the injection site (local allergic reaction)**. You may get redness, swelling, and itching at the injection site. If you keep having skin reactions or they are serious talk to your healthcare provider. You may need to stop using NovoLog and use a different insulin. Do not inject insulin into skin that is red, swollen, or itchy.
- **Skin thickens or pits at the injection site (lipodystrophy).** Change (rotate) where you inject your insulin to help to prevent these skin changes from happening. Do not inject insulin into this type of skin.
- **Swelling of your hands and feet.**
- **Vision changes**
- **Low potassium in your blood (hypokalemia)**

- **Weight gain**

These are not all of the possible side effects from NovoLog. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NovoLog?

All Unopened NovoLog:

- **Keep all unopened NovoLog in the refrigerator between 36° to 46°F (2° to 8°C).**
- Do not freeze. Do not use NovoLog if it has been frozen.
- Keep unopened NovoLog in the carton to protect from light.

NovoLog in use:

- **Vials.**
  - Keep in the refrigerator or at room temperature below 86°F (30°C) for up to 28 days.
  - Keep vials away from direct heat or light.
  - Throw away an opened vial after 28 days of use, even if there is insulin left in the vial.
  - Do not draw up NovoLog into a syringe and store for later use
  - Unopened vials can be used until the expiration date on the NovoLog label, if the medicine has been stored in a refrigerator.

- **PenFill Cartridges or NovoLog FlexPen Prefilled syringe.**
  - Keep at room temperature below 86°F (30°C) for up to 28 days.
  - Do not store a PenFill cartridge or NovoLog FlexPen Prefilled syringe that you are using in the refrigerator.
  - Keep PenFill cartridges and NovoLog FlexPen Prefilled syringe away from direct heat or light.
  - Throw away a used PenFill cartridge or NovoLog FlexPen Prefilled syringes after 28 days, even if there is insulin left in the cartridge or syringe.

- **NovoLog in the pump reservoir and the complete external pump infusion set**

- The reservoir, tubing, and catheter-needle should be changed **at least every 48 hours**. Change more often than every 48 hours if you have high blood sugar (hyperglycemia), the pump alarm sounds, or the insulin flow is blocked (occlusion).

General advice about NovoLog
Medicines are sometimes prescribed for conditions that are not mentioned in the patient leaflet. Do not use NovoLog for a condition for which it was not prescribed. Do not give NovoLog to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about NovoLog. If you would like more information about NovoLog or diabetes, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about NovoLog that is written for healthcare professionals. Call 1-800-727-6500 or visit www.novonordisk-us.com for more information.

Helpful information for people with diabetes is published by the American Diabetes Association, 1660 Duke Street, Alexandria, VA 22314 and on www.diabetes.org.

NovoLog® ingredients include:

- insulin aspart
- glycerin
- phenol
- metacresol
- zinc
- disodium hydrogen phosphate dihydrate
- sodium chloride

All NovoLog vials, PenFill cartridges and NovoLog FlexPen Prefilled syringes are latex free.

Date of Issue: March 14, 2008
Version: 6

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

For information about NovoLog® contact:
Novo Nordisk Inc.
100 College Road West,
Princeton, New Jersey 08540

Patient Instructions for Use
NovoLog® FlexPen® Prefilled syringe

How to use the NovoLog FlexPen Prefilled syringe

The NovoLog FlexPen Prefilled syringe is a disposable insulin delivery system. NovoLog FlexPen Prefilled syringe should be used with NovoFine® single use needles. The NovoLog FlexPen Prefilled syringe should not be used by people who are blind or have severe vision problems without the help of a person who has good eyesight and who is trained to use the Prefilled syringe the right way.

Please read these instructions completely before using this device.

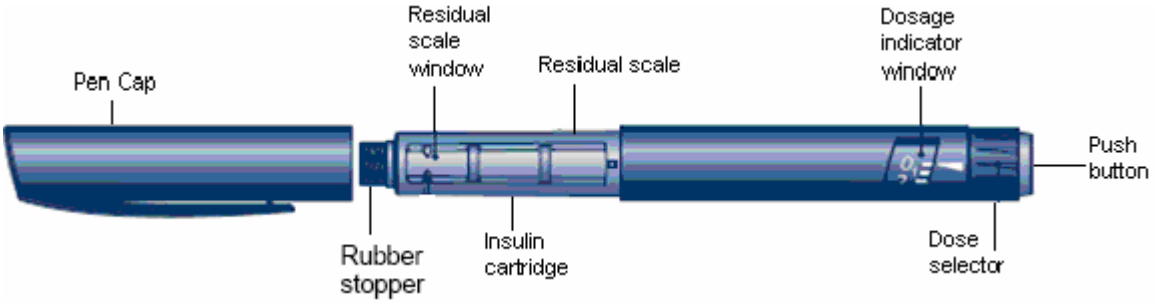


Diagram A FlexPen Prefilled Syringe

NovoFine® needle

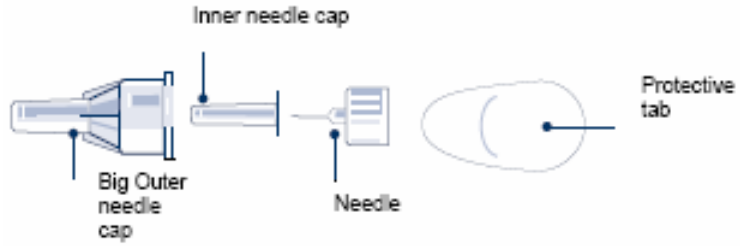
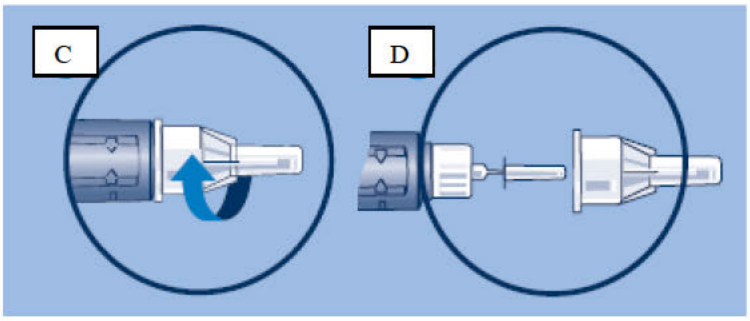


Diagram B NovoFine needle

1. PREPARING THE NOVOLOG FLEXPEN PREFILLED SYRINGE

Wash your hands with soap and water. Before you start to prepare your injection, check the label to make sure that you are taking the right type of insulin. This is especially important if you take more than 1 type of insulin. NovoLog should look clear.

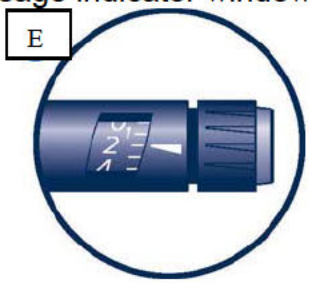
- Pull off the pen cap.
- Wipe the rubber stopper with an alcohol swab.
- Remove the protective tab from the disposable needle and screw the needle tightly onto the NovoLog FlexPen Prefilled syringe (see diagram A and B). Do not place a disposable needle on your NovoLog FlexPen Prefilled syringe until you are ready to take your injection.



- Pull off the outer and inner needle caps (see diagram C and D). Do not throw away the big outer needle cap.

Giving the airshot before each injection:
Small amounts of air may collect in the needle and insulin cartridge during normal use. To avoid injecting air and to make sure you take the right dose of insulin, do the following:

- Dial 2 units by turning the dose selector so that the arrow lines up with the "2" in the dosage indicator window (see diagram E below).

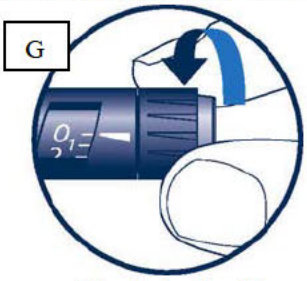


- **Hold the NovoLog FlexPen Prefilled syringe with the needle pointing up. Tap the insulin cartridge gently with your finger a few times (see diagram F).** A small air bubble may remain but it will not be injected. The NovoLog FlexPen Prefilled syringe prevents the cartridge from being completely emptied.

- Keep the needle pointing up and press the push button (on the end of the FlexPen) all the way in. You should see a drop of insulin at the needle tip. If you do not see a drop of insulin, repeat these steps: dial 2 units, tap the insulin cartridge and press the push button, until insulin appears. You may need to do this up to 6 times. If you don't see a drop of insulin after 6 times, do not use the NovoLog FlexPen Prefilled syringe and contact Novo Nordisk at 1-800-727-6500.

2. SETTING THE DOSE

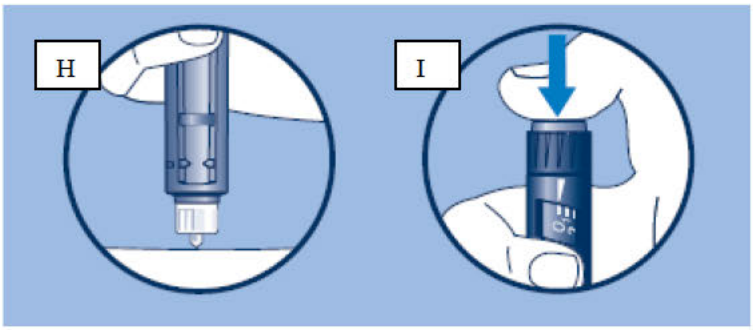
- Check and make sure that the dose selector is set at zero (0) (see diagram G).



- Dial the number of units you need to inject. **The arrow should line up with your dose.**
- The dose can be corrected by turning the dose selector in either direction. When dialing back, be careful not to press the push button, this will cause the insulin to come out. You can not set a dose larger than the number of units left in the cartridge. You will hear a click for every single unit dialed. Do not set the dose by counting the number of clicks you hear.

3. GIVING THE INJECTION

Do the injection exactly as shown to you by your healthcare provider.



- If you clean your injection site with an alcohol swab, let the injection site dry before you inject.
- Insert the needle into the skin. Push the needle into the skin (see diagram H).
- Give the dose of insulin by pressing the push button all the way in (see diagram I). Be careful to only press the button when injecting.
- Keep the needle in the skin for at least 6 seconds, and keep the push button pressed all the way in until the needle has been pulled out from the skin. This will make sure that the full dose has been given. You may see a drop of NovoLog at the needle tip. This is normal and has no effect on the dose you just received..If blood appears after you take the needle out of your skin, press the injection site lightly with a finger. **Do not rub the area.**

After the injection

- **Do not recap the needle.** Recapping can lead to a needle stick injury. Remove the needle from the NovoLog FlexPen Prefilled syringe after each injection. This

helps to prevent infection, and leakage of insulin, and will help to make sure you inject the right dose of insulin. Put the needle and any empty NovoLog FlexPen Prefilled syringes or any used NovoLog FlexPen Prefilled syringe still containing insulin in a sharps container, or some type of hard plastic or metal container with a screw top such as a detergent bottle or coffee can. These containers should be sealed and thrown away the right way. Check with you doctor about the right way to throw away used syringes and needles. There may be local or state laws about how to throw away used needles and syringes. Do not throw away used needles and syringes in household trash or recycling bins.

- Put the pen cap on the NovoLog FlexPen Prefilled syringe and store the NovoLog FlexPen Prefilled syringe without the needle attached.

Health care providers, relatives and other caregivers should follow general precautions for removing and disposing of needles to lessen the chance of a needle stick injury.

4. FUTURE INJECTIONS

It is important that you use a new needle for each injection. Follow the directions in steps 1, 2, and 3 above.

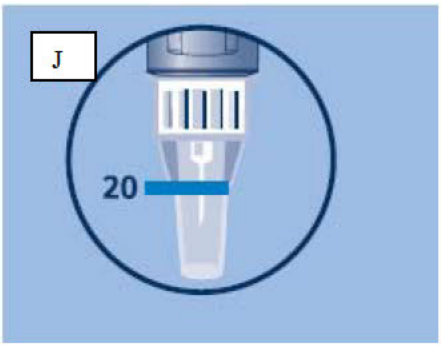
The numbers on the insulin cartridge can be used to estimate the amount of insulin left in the NovoLog FlexPen Prefilled syringe. Do not use these numbers to measure the insulin dose. You cannot set a dose more than the number of units remaining in the cartridge.

5. FUNCTION CHECK

If your NovoLog FlexPen Prefilled syringe is not working the right way, follow this procedure:

- Screw on a new NovoFine needle
- Do an airshot as described in step 1.
- Put the outer needle cap onto the needle. Do not put on the inner needle cap.
- Turn the dose selector so the dose indicator window shows 20 units.
- Hold the NovoLog FlexPen Prefilled syringe so the needle is pointing down
- Press the push button all the way in.

The insulin should fill the lower part of the big outer needle cap (see diagram J). If the NovoLog FlexPen Prefilled syringe has released too much or too little insulin, do the function check again. If the same problem happens again, do not use your NovoLog FlexPen Prefilled syringe and contact Novo Nordisk at 1-800-727-6500.



6. IMPORTANT NOTES

- If you need to perform more than 6 airshots before the first use of each NovoLog FlexPen Prefilled syringe to get a drop of insulin at the needle tip, do not use the NovoLog FlexPen Prefilled syringe and contact Novo Nordisk at 1-800-727-6500.
- Remember to perform an air shot before each injection. See diagrams E and F..
- Do not drop the NovoLog FlexPen Prefilled syringe.
- Keep the NovoLog FlexPen Prefilled syringe with you. Do not leave it in a car or other place where it can get too hot or too cold.
- NovoLog FlexPen Prefilled syringe should be used with NovoFine disposable needles.
- Novo Nordisk is not responsible for harm due to using this insulin delivery system with products not recommended by Novo Nordisk.
- Do not put a disposable needle on the NovoLog FlexPen Prefilled syringe until you are ready to use it. Remove the needle right after use. Do not recap the needle.
- Throw away the used NovoLog FlexPen Prefilled syringe without the needle attached.
- Always carry an extra NovoLog FlexPen Prefilled syringe with you in case the NovoLog FlexPen Prefilled syringe is damaged or lost.
- Keep your NovoLog FlexPen Prefilled syringe and needles out of the reach of children. Use NovoLog FlexPen Prefilled syringe as directed to treat your diabetes. Do not share it with anyone else even if they also have diabetes.

Patient Instructions for Use
NovoLog® 3 mL PenFill® cartridge (100 Units/mL, U-100)

Before using the NovoLog cartridge

1. Talk with your healthcare provider for information about where to inject NovoLog (injection sites) and how to give an injection with your insulin delivery device.
2. Read the instruction manual that comes with your insulin delivery device for complete instructions on how to use the PenFill cartridge with the device.

How to use the NovoLog cartridge

1. **Check your insulin**. Just before using your NovoLog cartridge, check to make sure that you have the right type of insulin. This is especially important if you use different types of insulin.
2. **Carefully look at the cartridge and the insulin inside it**. The insulin should be clear and colorless. The tamper-resistant foil should be in place before the first use. If the foil has been broken or removed before your first use of the cartridge, or if the insulin is cloudy or colored, do not use it. Call Novo Nordisk at 1-800-727-6500.
3. **Wash your hands** well with soap and water. If you clean your injection site with an alcohol swab, let the injection site dry before you inject. Talk with your healthcare provider for guidance on injection sites and how to give an injection with your insulin delivery device.
4. Gather your supplies for injecting NovoLog.
5. Insert a 3 mL cartridge into your Novo Nordisk 3 mL PenFill cartridge compatible insulin delivery device. Wipe the front rubber stopper of the 3 mL PenFill cartridge with an alcohol swab, then screw on a new needle. For NovoFine needles, remove the big outer needle cap and the inner needle cap. Always use a new needle for each injection to prevent infection.

Giving the airshot before each injection:

To prevent the injection of air and to make sure insulin is delivered, you must do an air shot before each injection. Hold the device with the needle pointing up and gently tap the PenFill® cartridge holder with your finger a few times to raise any air bubbles to the top of the cartridge. Do the air shot as described in the device instruction manual.

Giving the injection

6. Dial the number of units on the insulin delivery device that you need to inject. Inject the right way as shown to you by your healthcare provider.
7. Insert the needle into the skin. Inject the dose by pressing the push button all the way in. Keep the needle in the skin for at least 6 seconds, and keep the push button pressed all the way in until the needle has been pulled out from the skin. This will make sure that the full dose has been given. You may see a drop of NovoLog at the needle tip. This is normal and has no effect on the dose you just received If blood appears after you take the needle out of your skin, press the injection site lightly with a finger. **Do not rub the area.**

After the injection

8. **Do not recap the needle.** Recapping can lead to a needle stick injury.
9. Remove the needle from the PenFill cartridge after each injection. Keep the 3 mL PenFill cartridge in the insulin delivery device. The needle should not be attached to the 3 mL PenFill cartridge during storage. This will prevent infection or leakage of insulin and will help ensure that you receive the right dose of NovoLog.
10. Put the used needle and cartridge in a sharps container, or some type of hard plastic or metal container with a screw on top such as a detergent bottle or coffee can. Check with your doctor about the right way to throw away used needles and cartridges. There may be local or state laws about how to throw away used needles and syringes. Do not throw used needles and cartridges in household trash or recycling bins.
11. Put the pen cap back on the Novo Nordisk 3 mL PenFill cartridge compatible insulin delivery device.

Patient Instructions for Use
NovoLog® 10 mL vial (100 Units/mL, U-100)

Before starting, gather all of the supplies that you will need to use for preparing and giving your insulin injection.

Never re-use syringes and needles.

How should I use the NovoLog vial?

1. Check to make sure that you have the correct type of insulin. This is especially important if you use different types of insulin.
2. Look at the vial and the insulin. The insulin should be clear and colorless. The tamper-resistant cap should be in place before the first use. If the cap had been removed before your first use of the vial, or if the insulin is cloudy or colored, do not use it and call Novo Nordisk at 1-800-727-6500
3. Wash your hands with soap and water. If you clean your injection site with an alcohol swab, let the injection site dry before you inject. Talk with your healthcare provider about how to rotate injection sites and how to give an injection.
4. If you are using a new vial, pull off the tamper-resistant cap. Wipe the rubber stopper with an alcohol wipe.
5. Do not roll or shake the vial. Shaking right before the dose is drawn into the syringe may cause bubbles or froth. This can cause you to draw up the wrong dose of insulin.
6. Pull back the plunger on the syringe until the black tip reaches the marking for the number of units you will inject.
7. Push the needle through the rubber stopper of the vial, and push the plunger all the way in to force air into the vial.
8. Turn the vial and syringe upside down and slowly pull the plunger back to a few units beyond correct dose.
9. If there are any air bubbles, tap the syringe gently with your finger to raise the air bubbles to the top. Then slowly push the plunger to the marking for your correct dose. This process should move any air bubbles present in the syringe back into the vial.
10. Check to make sure you have the right dose of NovoLog in the syringe.
11. Pull the syringe out of the vial's rubber stopper.
12. Your doctor should tell you if you need to pinch the skin before inserting the needle. This can vary from patient to patient so it is important to ask your doctor if you did not receive instructions on pinching the skin. Insert the needle into the pinched skin. Press the plunger of the syringe to inject the insulin. When you are finished injecting the insulin, pull the needle out of your skin. You may see a drop of NovoLog at the needle tip. This is normal and has no effect on the dose you just received. If you see blood after

you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol wipe. **Do not rub the area.**

13. After your injection, do not recap the needle. Place used syringes, needles and used insulin vials in a disposable puncture-resistant sharps container, or some type of hard plastic or metal container with a screw on cap such as a detergent bottle or coffee can.
14. Ask your healthcare provider about the right way to throw away used syringes and needles. There may be state or local laws about the right way to throw away used syringes and needles. Do not throw away used needles and syringes in household trash or recycle.

How should I mix insulins?

NovoLog should be mixed only when injections with syringes are used. NovoLog can be mixed with NPH human insulin right before use. The NovoLog should be drawn into the syringe before you draw up the NPH insulin. **NovoLog should not be mixed with any other insulin except NPH.**

1. Add together the doses (total number of units) of NPH and NovoLog that you need to inject. The total dose will determine the final amount (volume) in the syringe after drawing up both insulins into the syringe. For example, if you need 5 units of NPH and 2 units of NovoLog, the total dose of insulin in the syringe would be 7 units.
2. Roll the NPH vial between your hands until the liquid is equally cloudy throughout.
3. Draw into the syringe the same amount of air as the NPH dose. Inject this air into the NPH vial and then remove the needle from the vial but do not withdraw any of the NPH insulin. (Transferring NPH to the NovoLog vial will contaminate the NovoLog vial and may change how quickly it works.)
4. Draw into the syringe the same amount of air as the NovoLog dose. Inject this air into the NovoLog vial. With the needle in place, turn the vial upside down and withdraw the correct dose of NovoLog. The tip of the needle must be in the NovoLog to get the full dose and not an air dose.
5. After withdrawing the needle from the NovoLog vial, insert the needle into the NPH vial. Turn the NPH vial upside down with the syringe and needle still in it. Withdraw the correct dose of NPH.
6. Inject right away to avoid changes in how quickly the insulin works.

How do I use NovoLog in a pump?

- Checking your blood sugar is very important for patients using pumps. Pump or infusion set problems can result in you not getting enough insulin. This can quickly cause you to have high blood sugar and diabetic ketoacidosis.
- Use insulin from a new vial of NovoLog if unexplained high blood sugar or pump alarms do not respond to all of the following:

  - a repeat dose (injection or bolus) of NovoLog
  - a change in the infusion set, including the NovoLog in the reservoir
  - a change in the infusion site
- If these measures do not work, you may need to go back to injecting NovoLog with syringes, or insulin pens. Continue to monitor your blood sugars and ketones. If problems continue, you must contact your healthcare provider.
- When NovoLog is used in pumps, **use only pumps that are recommended by your healthcare provider.** The reservoir, infusion set, and injection site should be changed at least every 48 hours. The reservoir, the infusion set, and infusion site should also be changed:
  - with unexpected high blood sugar
  - when the alarm sounds (see your pump manual)
  - if the insulin or pump has been exposed to temperatures over 98.6°F (37°C), such as in a sauna, with long showers, or on an unusually hot day.
  - if the insulin or pump could have absorbed heat, for example from sunlight, that would heat the insulin to over 98.6°F (37°C). Dark colored pump cases or sport covers can increase this type of heat. The location where the pump is worn may also affect the temperature

Patients who develop “pump bumps” (skin reactions at the infusion site) may need to change infusion sites more often than every 48 hours.

NovoLog is recommended for use with MiniMed 500 series, or other pumps recommended by your doctor.

1. Check to make sure that you have the right type of insulin.
2. Look at the vial and insulin. The insulin should be clear and colorless. The tamper-resistant cap should be in place before the first use. If the cap had been removed before your first use, or if the insulin is cloudy or colored, do not use it and call Novo Nordisk at 1-800-727-6500.
3. Wash your hands with soap and water.
4. Fill the reservoir-syringe with 2 days worth of NovoLog plus about 25 extra units to prime the pump and the infusion tubing.
5. Remove air bubbles from the reservoir by following the pump manufacturers’ instructions.
6. Attach the infusion set to the reservoir. Make sure the connection is tight. Prime the infusion set until you see a drop of insulin coming out of the infusion needle-catheter. Follow the pump manufacturers’ instructions for priming and removing air bubbles.
7. Clean your insertion site with an alcohol swab and let the site dry before you insert the needle-catheter. Talk with your healthcare provider about how to rotate insertion sites and how to insert the needle-catheter into the skin.

8. Insert the needle-catheter into the skin, remove the needle and prime the catheter according to the pump manufacturers' instructions. Do not insert the needle-catheter into skin that is reddened, itchy, bumpy, or thickened.
9. Program the pump for mealtime NovoLog boluses and NovoLog basal insulin infusion according to instructions from your healthcare provider and the manufacturer of your pump equipment.
10. Change the infusion site, the insulin reservoir, the tubing, the catheter-needle, and the insulin every 48 hours or less, even if you have not used all of the insulin. This will help ensure that NovoLog and the pump work well.
11. Change the infusion site, the insulin reservoir, the tubing, the catheter-needle, and the insulin if you experience a pump alarm, catheter blockage, high blood sugars, or if your pump insulin has been exposed to heat greater than 98.6^{o}F (37^{o}C).
12. If you have high blood sugar (hyperglycemia) when you check your blood sugar, this may be the first sign of a problem with the pump, infusion set, or NovoLog. If you have high blood sugar without a pump alarm, you must still check the pump because alarms may not detect all the changes to NovoLog that could result in high blood sugar. You may need to start insulin injections with syringes if the cause of the problem cannot be found quickly or fixed. Long lengths of infusion-set tubing increase the risk for kinking and expose the insulin in the tubing to more changes in temperature.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020986/S-047

MEDICAL REVIEW(S)

MEDICAL TEAM LEADER MEMO
Completed 11-March-2008

Hylton V. Joffe, M.D., M.M.Sc.

NDA: 20-986 (S-047)
Sponsor: Novo Nordisk
Drug: NovoLog (insulin aspart)
Indication: Treatment of diabetes mellitus
Intended Population: Children with type 1 diabetes (b) (4)
Primary Medical Reviewer: Joanna Zawadzki, M.D.

I. INTRODUCTION AND BACKGROUND

Insulin aspart (NovoLog) and lispro (Humalog) are commonly used in insulin pumps to treat type 1 diabetes in children. Novo Nordisk, the Sponsor of aspart, conducted the current insulin pump study to compare aspart and lispro head-to-head in this patient population and to fulfill a postmarketing commitment for aspart under PREA (Pediatric Research Equity Act).

Both aspart and lispro have been FDA-approved for subcutaneous injection in adults and children with diabetes and both insulins are FDA-approved for pump use in adults. During the design phase of the current study, the FDA recommended a comparison between aspart and Velosulin buffered human insulin (regular human insulin), because Velosulin was the only insulin approved for pump use at that time. Novo Nordisk instead waited to initiate the current study until after the FDA approved lispro for pump use in adults. The choice to compare aspart to lispro is appropriate, because these insulin analogs have become standard-of-care treatments for type 1 diabetes and share similar pharmacokinetic and pharmacodynamic properties.

II. CLINICAL STUDIES

A. 2181: "External Continuous Subcutaneous Infusion of Insulin Aspart (NovoLog) versus Insulin Lispro (Humalog): An Open-Label, Randomised, Parallel Group, Multicentre Study in Children and Adolescents with Type 1 Diabetes"

1. Objectives: To compare aspart and lispro in children and adolescents with type 1 diabetes using insulin pump therapy.

- Primary: Change in HbA1c from baseline

- Secondary: Included self-monitored blood glucose (SMBG), responder analyses (e.g., HbA1c <7.0%), and safety (hypoglycemia, diabetic ketoacidosis, hyperglycemia, insulin antibodies, infusion site reactions)

2. Study design: Multicenter (all 45 sites in the United States), open-label, randomized, active controlled, parallel group non-inferiority study. Patients were randomized 2:1 to aspart or lispro administered via insulin pump for 16 weeks. The insertion site was directed by the investigator and could include the abdominal wall, lower back, hips, and thighs. The reservoir, infusion set, and infusion site were to be changed at least once every 48 hours. Randomization was stratified by age (3-5 years; 6-11 years; 12-18 years).

Reviewer's comments: The open-label design is not ideal for a non-inferiority trial, because differential management of glycemia could bias results towards non-inferiority. That said, active-controlled insulin trials have traditionally had open-label designs because of difficulty blinding insulin therapies.

Clinic visits occurred every 2 weeks. Telephone communication occurred on Weeks 1, 3, 6, 10, 14, and 17.

Study assessments included:
- Vital signs and body weight at all clinic visits
- Review of hypoglycemic events and adjustments in insulin dose at all visits
- Insulin antibodies and fasting plasma glucose (FPG) at Weeks 0 and 16
- Hematology, biochemistry, urinalysis and pregnancy test at Weeks -2 and 16
- HbA1c at Weeks -2, 8, 12 and 16
- 4-point SMBG and total 24 hour insulin dose collected on two days prior to each office visit (SMBG was used to adjust the insulin dose)
- 8-point SMBG on two days within 72 hours of the Week 0 and 16 visits

Reasons for withdrawal from the study could include:
- An unexplained episode of diabetic ketoacidosis
- Frequent, unexplained episodes of minor hypoglycemia (plasma glucose ≤56 mg/dL or symptomatic episodes without a recorded glucose measurement) or >1 episode of severe hyperglycemia (plasma glucose ≤56 mg/dL requiring assistance from a third party)
- Initiation of medication influencing glucose homeostasis (e.g., glucocorticoids)

3. Treatments: Study medication was administered via each patient's own insulin pump. Investigators were to titrate study medication to achieve age-specific glycemic targets using daily SMBG profiles (Table 1). Investigators assessed compliance by estimating the total administered dose of study medication since the prior visit based on partially used and unused insulin vials.

Table 1. Age-Specific Glycemic Targets			
Time	**Plasma blood glucose range (mg/dL)**		
	Ages 3-5	**Ages 6 – 11**	**Ages 12 - 18**
Preprandial	80-180	80 − 180	80 − 150
2-hr postprandial	<180	< 180	<160
Bedtime	120-180	120-180	110-160

4. Study population:

Major inclusion criteria included:

- Age 3-18 years with type 1 diabetes for at least 1 year prior to enrollment
- Treatment with aspart or lispro via an FDA-approved insulin pump (only certain models were permitted) for ≥3 months
- HbA1c ≤10% on a stable insulin dose for ≥2 weeks
- Signed informed consent by parent/legal guardian and child assent (if applicable). Patients 18 years of age signed the consent form and did not require parental consent

Major exclusion criteria included:

- Chronic use of adrenal suppressive doses of glucocorticoids
- History of active proliferative retinopathy
- Recurrent, severe hypoglycemia or hypoglycemia unawareness
- Insulin basal rate ≤0.05 units/hour or use of diluted insulin
- Laboratory abnormalities exceeding pre-defined criteria (e.g., serum creatinine >upper limit of normal, ALT >2x upper limit of normal)

5: Efficacy endpoints: The primary efficacy endpoint was the change in HbA1c from baseline (Week -2) to Week 16.

Secondary efficacy endpoints included 4-point SMBG profiles and the total daily insulin dose collected over two days prior to each office visit.

6. Statistics: The primary conclusion regarding non-inferiority was based on the intent-to-treat population (all randomized patients who received at least one dose of study medication). To assess robustness of the results, the Sponsor also analyzed the primary efficacy endpoint using the per-protocol population (randomized patients with no significant deviations from the study protocol).

The primary endpoint was analyzed using an ANCOVA model with treatment and age group as fixed effects and baseline HbA1c as a covariate. Missing values were imputed using last observation carried forward. The pre-specified non-inferiority margin was 0.4%, which has been accepted by FDA for other active-controlled trials testing insulin therapies. Therefore, non-inferiority would be concluded if the upper limit of the 95% confidence interval for the difference of the two treatments (aspart minus lispro) was greater than 0.4%. The Sponsor

would conclude superiority if the lower limit of the 95% confidence interval for this difference was greater than 0%.

The Sponsor estimated that enrollment of 282 patients would have 80% power to show non-inferiority with a margin of 0.4% assuming a drop-out rate of 17%, a standard deviation for change in HbA1c of 1.025%, and a one-sided alpha of 0.025.

B. 1507: "A Multicentre open label 29 weeks three armed efficacy and safety study with two arms randomized and one arm fixed allocation to CSII comparing insulin NovoRapid multiple injection or CSII with Actrapid multiple injection in diabetes type 1 children below 7 years of age"

1. Primary objective: To compare the efficacy of aspart via multiple daily injections or via insulin pump to regular human insulin via multiple daily injections in children <7 years of age with type 1 diabetes.

2. Study design: This was a multicenter, open label, three-arm trial in 61 children <7 years of age with type 1 diabetes of at least 1-year duration. Patients who enrolled in the study underwent a 3-week run-in period on regular human insulin and NPH. At the end of this run-in period, two-thirds of the patients were randomized to either continue the regular human insulin + NPH injections (n=21) or switch to aspart + NPH injections (n=20). The remaining patients (n=20) were administered aspart via insulin pump. The insulin pump arm was not randomized; instead, patients were assigned to this treatment regimen based on the discretion of the investigators. The investigator was to adjust the pump regimen "according to his/her best knowledge".

Visits occurred at screening, randomization (Week 3), Week 16, and Week 29.

Reviewer's comments: Because the use of pump therapy was not randomized in this trial, assignment to this treatment was likely biased (e.g., investigators could identify candidates who were most likely to succeed using this therapy). Therefore, conclusions from this study are limited and the efficacy and safety results from the insulin pump arm cannot be directly compared to the results from the insulin injection arms. For this reason, the information from this trial is at best supportive of the data in Study 2181. As such, I will focus mostly on the safety information from the non-randomized insulin pump arm. Please see Dr. Zawadzki's review and the clinical study report for further details.

III. CLINICAL EFFICACY FOR STUDY 2181

1. Disposition: A total of 198 patients were randomized to aspart and 100 patients were randomized to lispro (Table 2). Twenty patients withdrew from the

study (6% of the aspart group and 9% of the lispro group). Most of these withdrawals were due to non-compliance or withdrawal of consent. Only 1 patient withdrew due to an adverse event (see the safety section of this memo for details).

Table 2. Patient Disposition		
	Apart N (%)	**Lispro N (%)**
Enrolled	198	100
Randomized	198	100
Withdrawals	11 (5.6)	9 (9.0)
Adverse event	0	1 (1.0)
Non-compliance	8 (4.0)	6 (6.0)
Withdrawal of consent	3 (1.5)	1 (1.0)
Other	0	1 (1.0)*
Completers	187 (94.4)	91 (91.0)
*Required prohibited concomitant medication		

2. Demographics:

The randomized patients had a mean age of 13 years, mean body mass index of 21.7-21.8 kg/m^2, and mean baseline HbA1c of 8.0-8.1%. At baseline, the mean duration of pump use was ~30 months and the mean duration of diabetes was ~6 years. Slightly more than one-half of the patients were using lispro and the remainder was using aspart (Table 3). Most of the patients were Caucasian, and approximately one-half were boys.

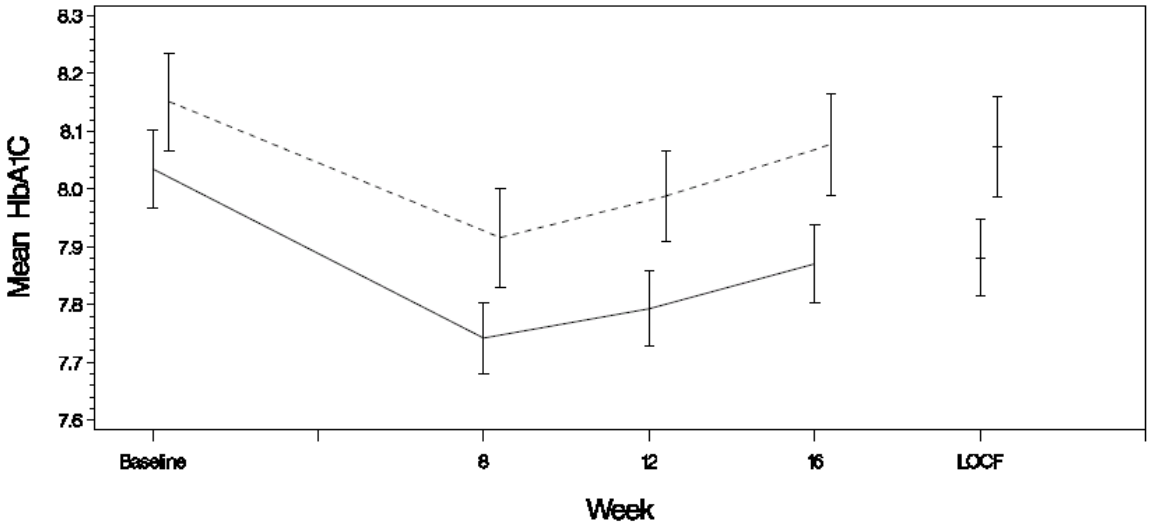
Table 3. Baseline demographics (all randomized patients)		
	Apart (N=198)	**Lispro (N=100)**
Male gender, n (%)	95 (48.0)	48 (48.0)
Race/ethnicity, n (%)		
Caucasian	180 (90.9)	94 (94.0)
Black	11 (5.6)	2 (2.0)
Other	7 (3.5)	4 (4.0)
Age (yrs)	13±3 (4-18)	13±3 (4-18)
Body mass index (kg/m^2)	21.7±4.4	21.8±4.4
Fasting plasma glucose (mg/dL)	171±78	176±67
HbA1c (%)	8.0±0.9	8.1±0.8
Duration of diabetes (yrs)	6.1±3.4	6.0±2.8
Current diabetes therapy, n (%)		
Aspart	87 (43.9)	44 (44.0)
Lispro	111 (56.1)	56 (56.0)
Type of insulin pump, n (%)		
MiniMed 511	52 (26.3)	26 (26.0)
MiniMed 512	59 (29.8)	36 (36.0)
MiniMed 712	43 (21.7)	17 (17.0)
Other	44 (22.2)	21 (21.0)
Duration of insulin pump (wks)	121±80	133±70
Total daily insulin dose (units)	50±24	53±24
Plus-minus values are mean±SD		

3. Primary efficacy endpoint: The mean baseline HbA1c was 8.0% in the aspart group and 8.2% in the lispro group. The LS mean change in HbA1c from baseline to study end was -0.2% with aspart and -0.1% with lispro. The 95% confidence interval for the change in HbA1c with aspart relative to lispro was -0.3% to 0.1% (Table 4). Therefore, aspart is non-inferior to lispro with regard to change in HbA1c because the upper limit of this 95% confidence interval is less than the pre-specified non-inferiority margin of 0.4%. The per-protocol population (20 fewer aspart-treated patients and 16 fewer lispro-treated patients) yielded virtually identical results. Two patients (both receiving lispro) were found to have treatment non-compliance and were among those patients excluded from the per-protocol analysis.

Table 4. Change in HbA1c from baseline				
	N	Baseline HbA1c (%) mean (SD)	Change in HbA1c (%) LS mean (SE)	Aspart – Lispro Mean (95% confidence interval)
Intent-to-treat population				
Aspart	192	8.0 (0.9)	-0.2 (0.1)	-0.1 (-0.3, 0.1); p=0.24
Lispro	96	8.2 (0.8)	-0.1 (0.1)	
Per-protocol population				
Aspart	172	8.0 (0.9)	-0.2 (0.1)	-0.1 (-0.3, 0.1); p=0.30
Lispro	80	8.1 (0.8)	-0.1 (0.1)	

The mean HbA1c values for both treatment groups nadired at Week 8 then slowly increased at Weeks 12 and Weeks 16, approaching baseline values (Figure 1). The reason for this loss of efficacy after the mid-point of the trial is unclear. One potential explanation could be easing of glycemic control by investigators to prevent hypoglycemia.

Figure 1. HbA1c over time (mean±SE) – intent-to-treat population



Solid line = aspart; dashed line = lispro; LOCF = last observation carried forward

4. Select secondary efficacy endpoints:

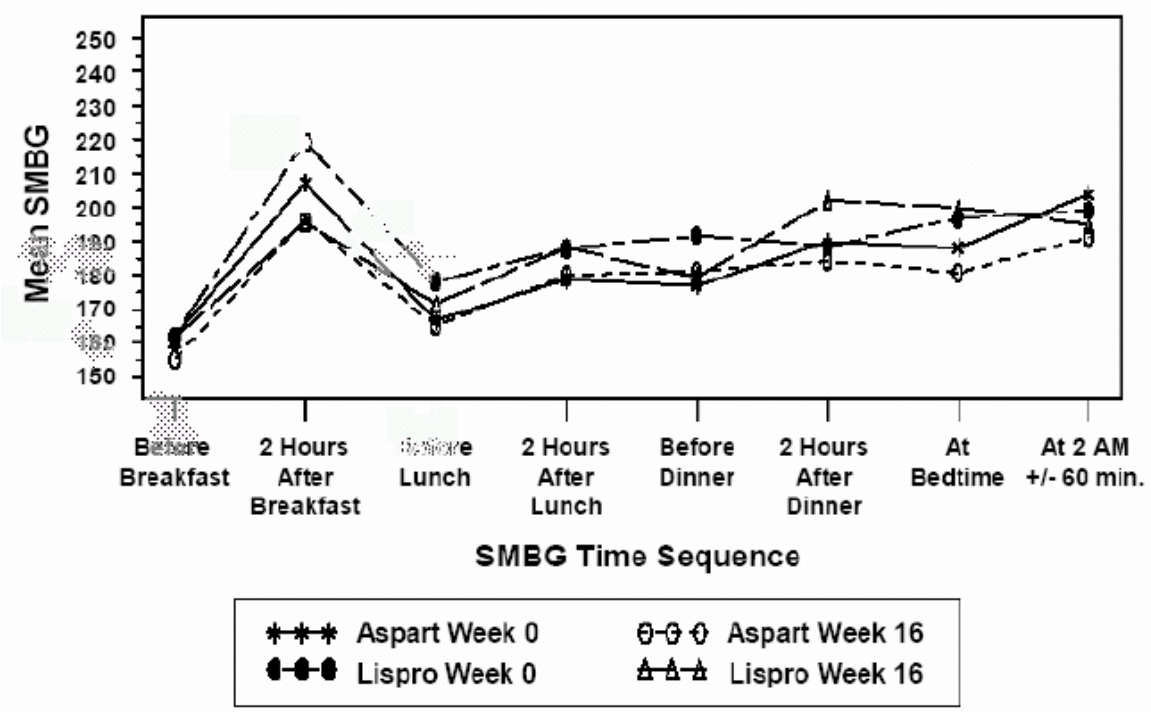
HbA1c targets: The baseline mean HbA1c was slightly lower in the aspart group (8.0%) compared to the lispro group (8.2%). This discrepancy likely contributes to the numerically higher proportion of aspart-treated patients reaching HbA1c goals compared to lispro-treated patients (Table 5). None of the comparisons for the pre-specified HbA1c targets of ≤6.5% and <7% were statistically significant at the alpha=0.05 level (p=0.3-1.0). As a post-hoc analysis, the Sponsor calculated

the proportion of patients in each group meeting age-specific HbA1c targets, as defined in the 2004 American Diabetes Association Clinical Practice Guidelines. In this analysis (Table 5), only the comparison of aspart (59.7%) to lispro (43.8%) at Week 16 reached statistical significance (p=0.01).

Table 5. Patients meeting HbA1c targets		
	Aspart n/N (%)	**Lispro n/N (%)**
HbA1c ≤6.5%		
Week 8	7/189 (3.7)	2/95 (2.1)
Week 12	10/183 (5.5)	5/92 (5.4)
Week 16	10/186 (5.4)	3/90 (3.3)
HbA1c <7%		
Week 8	27/189 (14.3)	9/95 (9.5)
Week 12	26/183 (14.2)	9/92 (9.8)
Week 16	23/186 (12.4)	8/90 (8.9)
HbA1c at age-specific target*		
Week 8	124/189 (65.6)	56/95 (58.9)
Week 12	113/182 (62.1)	46/90 (51.1)
Week 16	111/186 (59.7)	39/89 (43.8)
*Post-hoc analysis; HbA1c <8.5% for patients <6 years, <8% for patients 6-18 years		

Self-monitored blood glucoses: SMBG profiles were collected 8 times per day (prior to each meal, 2 hours after each meal, bedtime, and 2 a.m.) for two consecutive days prior to the baseline and Week 16 visits. Both treatment groups had similar profiles at these time points (Figure 2).

Figure 2. Mean 8-point SMBG values (mg/dL) at baseline and Week 16



Insulin dose: Total daily insulin dose was calculated based on insulin requirements during the two days prior to each office visit. At baseline, the aspart group had a slightly lower mean total daily insulin dose (49 units) compared to the lispro group (53 units). The mean total daily insulin dose at study end, whether measured in absolute units or in units per kg was essentially unchanged from the baseline values (Table 6).

Table 6. Insulin doses

	Aspart		Lispro	
	N	**Mean±SD**	**N**	**Mean±SD**
Total daily insulin dose (units)*				
Baseline	197	49±24	99	53±24
Week 16	187	49±25	92	54±25
Total daily insulin dose (units)*				
Baseline	197	0.9±0.3	99	0.9±0.2
Week 16	187	0.9±0.2	92	0.9±0.2
*2-day average				

5. Subgroup analyses based on age: The Sponsor analyzed the primary endpoint by the subgroups of age used for stratification. The results for the 6-11 year old age group and 12-18 year old age groups were consistent with the finding of non-inferiority in the overall treatment group. Conclusions for the 3-5

year old group were limited because of small sample sizes (7 aspart-treated patients and 3 lispro-treated patients).

Table 7. Change in HbA1c from baseline (subgroups of age) – intent-to-treat population				
	N	Baseline HbA1c (%) Mean (SD)	Change in HbA1c (%) Mean (SD)	Aspart – Lispro Mean (95% confidence interval)
3-5 years old				
Aspart	7	7.7 (0.9)	-0.2 (0.5)	0.1 (-0.8, 1.0)
Lispro	3	8.0 (0.5)	-0.4 (0.7)	
6-11 years old				
Aspart	54	7.9 (0.9)	-0.2 (0.6)	-0.2 (-0.4, 0.0)
Lispro	28	7.7 (0.7)	0.1 (0.5)	
12-18 years old				
Aspart	131	8.1 (1.0)	-0.1 (0.9)	-0.1 (-0.3, 0.2)
Lispro	65	8.4 (0.8)	-0.1 (0.8)	

6. Efficacy Conclusions:

This randomized, open-label, active-controlled, non-inferiority trial compared 16 weeks of treatment with aspart vs. lispro in children and adolescents (4-18 years old) with type 1 diabetes using insulin pump therapy.

The mean baseline HbA1c was 8.0% in the aspart group and 8.2% in the lispro group. The LS mean change in HbA1c from baseline to study end was -0.2% with aspart and -0.1% with lispro. Aspart was non-inferior to lispro based on the pre-specified non-inferiority margin of 0.4%.

The mean total daily insulin dose at study end, whether measured in absolute units or in units per kg was essentially unchanged from the baseline values.

Both treatment groups had a similar proportion of patients meeting the pre-specified HbA1c targets of ≤6.5% and <7% (p-value ≥0.3).

The Sponsor analyzed the primary endpoint by the subgroups of age used for stratification. The results for the 6-11 year old age group and 12-18 year old age group were consistent with the finding of non-inferiority in the overall treatment group. Conclusions for the 3-5 year old group were limited because of small sample sizes (7 aspart-treated patients and 3 lispro-treated patients).

IV. CLINICAL SAFETY

Unless stated otherwise, results in this section apply only to Study 2181.

1. Safety assessment: All patients who received at least one dose of randomized study medication were included in the safety assessments.

Adverse events were elicited from patients at each visit. The Sponsor used MedDRA Version 8.1 until April 2006 then used Version 9.0 thereafter. All adverse events that were originally coded with Version 8.1 were recoded using Version 9.0 prior to unblinding of the data.

Approximately 95% of the patients in each group were exposed to study medication for >12 weeks.

2. Deaths: There were no deaths.

3. Serious adverse events: Six patients (5 in the aspart group and 1 in the lispro group) reported treatment-emergent serious adverse events (Table 8). Narratives for these adverse events are summarized below:

Aspart: Patient (b) (6) – hypoglycemic seizure: 12-year old girl had an unprecipitated (e.g., no changes in diet or physical activity) early morning hypoglycemic seizure. Her HbA1c had improved from a baseline value of 8.0% to 6.2% (measured approximately 5 weeks after the hypoglycemic episode). She continued in the study.

Aspart: Patient (b) (6) – diabetic ketoacidosis: 13-year old girl developed mild diabetic ketoacidosis requiring a 3-hour visit to an emergency room after her insulin pump catheter became dislodged during her morning shower. This hyperglycemic episode occurred despite a morning subcutaneous injection of insulin (she chose not to insert a new infusion catheter). She continued in the study.

Aspart: Patient (b) (6) – hypoglycemia: 12-year old boy accidentally injected 5.5 units of aspart instead of the correct bolus of 1.5 units for a fingerstick glucose of 294 mg/dL, resulting in severe hypoglycemia leading to unconsciousness. He was treated with glucagon and fully recovered.

Aspart: Patient (b) (6) – hyperglycemia: 12-year old boy developed glucose measurements in the 400-600 mg/dL range associated with nausea and vomiting that resulted from kinking/occlusion of the catheter tubing. In the emergency room, his serum ketones were negative; therefore, diabetic ketoacidosis was not present. He recovered and continued in the study.

Aspart: Patient (b) (6) – skin laceration: 15-year old boy required sutures for a left leg laceration caused by sharp glass left in a walkway.

Lispro: Patient (b) (6) – hypoglycemia: 14-year old boy with a prior HbA1c of 6.4% had an episode of severe hypoglycemia leading to unconsciousness on Day 46 in the setting of gastroenteritis. His insulin dose was reduced for a few days.

Table 8. Serious Adverse Events			
Patient ID	**Event and day of onset**	**Severity**	**Action**
Aspart			
(b) (6)	Hypoglycemic seizure (Day 73)	Moderate	None*
	Diabetic ketoacidosis (Day 30)	Severe	None*
	Hypoglycemia (Day 25)	Severe	None*
	Hyperglycemia (Day 21)	Severe	Product withdrawn
	Skin laceration (Day 23)	Moderate	None*
Lispro			
(b) (6)	Hypoglycemia (Day 46)	Severe	Dose reduced
*Insulin dose was not changed			

4. Adverse events leading to withdrawal: Only 1 patient withdrew from the trial due to an adverse event. This patient was treated with lispro and requested to be discontinued after having persistent hyperglycemia due to repeated infusion set occlusions.

5. Adverse events: Table 9 summarizes the most common (incidence ≥5% in the aspart group) treatment-emergent adverse events in the trial. Approximately 80% of the patients in each group reported an adverse event. Only the following common adverse events occurred more frequently with aspart than with lispro: Nasopharyngitis (10.1% vs. 10.0%), headache (8.1% vs. 8.0%), pyrexia (6.1% vs. 4.0%), nausea (5.1% vs. 2.0%), and otitis media (5.1% vs. 2.0%).

Table 9. Common treatment-emergent adverse (incidence ≥5% in the aspart group)		
Preferred term	**Aspart N=198 n (%)**	**Lispro N=100 n (%)**
Patients with an adverse event	162 (81.8)	83 (83.0)
Upper respiratory tract infection	36 (18.2)	20 (20.0)
Nasopharyngitis	20 (10.1)	10 (10.0)
Vomiting	16 (8.1)	10 (10.0)
Headache	16 (8.1)	8 (8.0)
Pharyngolaryngeal pain	13 (6.6)	11 (11.0)
Infusion site reaction	12 (6.1)	7 (7.0)
Pyrexia	12 (6.1)	4 (4.0)
Infusion site erythema	11 (5.6)	6 (6.0)
Sinusitis	10 (5.1)	7 (7.0)
Nausea	10 (5.1)	2 (2.0)
Otitis media	10 (5.1)	2 (2.0)

6. Adverse events of special interest:

Hypoglycemia: Site staff reviewed the 4-point and 8-point SMBG profiles at each visit to identify hypoglycemic episodes. “Major hypoglycemia” was defined as an episode of severe central nervous system symptoms consistent with hypoglycemia requiring treatment by another person. “Minor hypoglycemia” was defined as a plasma glucose <56 mg/dL with or without symptoms that was self-treated. “Hypoglycemic symptoms” was defined as symptoms suggestive of hypoglycemia in patients without a corresponding glucose measurement or with an associated plasma glucose ≥56 mg/dL.

Most of the aspart and lispro-treated patients reported hypoglycemic episodes during the trial, although the majority of events were classified as minor. Approximately 10% of the patients in both groups had at least 1 major episode of hypoglycemia. In a post-hoc analysis, nearly one-half of the patients in each group had at least one recorded blood glucose ≤36 mg/dL.

Nocturnal hypoglycemia was reported in more than one-half of the patients in both treatment groups. Most of these episodes were minor. Although there were much fewer nocturnal episodes than daytime episodes, there may be reporting bias, because mild hypoglycemia may go undetected if the patient does not awaken.

Reviewer's comments: The incidence of major hypoglycemia in the current trial is slightly higher than that seen in the 24-week study of multiple daily injections of insulin in children with type 1 diabetes, particularly among the aspart-treated patients. In that trial, the incidence of severe hypoglycemia (as defined in the current study) was 6% with aspart + NPH (11/187) and 9% with buffered regular insulin + NPH group (9/96). However, the baseline HbA1c in the current study was lower than that in the multiple daily injection trial (8.0% vs. 8.3% for aspart; 8.2% vs. 8.3% for comparator), which likely contributes to the discrepant results with aspart.

Of note, in the 16-week insulin pump study in adults with type 1 diabetes and baseline HbA1c of 7.3-7.5%, the incidence of severe hypoglycemia (as defined in the current study) was 2% with aspart (1/60) and 3% with buffered human insulin (2/59). Children are at a higher risk for hypoglycemia than adults, as reflected by their higher glycemic targets in the American Diabetes Association Clinical Practice Guidelines.

Table 10. Hypoglycemia events						
	Aspart N=198 n (%)			Lispro N=100 n (%)		
	N (%)	Events	Rate per patient year	N (%)	Events	Rate per patient year
All	190 (96)	5547	92.2	97 (97)	2418	81.3
Major	19 (10)	25	0.4	8 (8)	9	0.3
Minor	188 (95)	4643	77.2	94 (94)	1961	66.0
Symptoms only	149 (75)	722	12.0	82 (82)	394	13.3
Unclassified	24 (12)	157	2.6	18 (18)	54	1.8
Blood glucose ≤36 mg/dL[1]	94 (48)	301	5.0	41 (41)	117	3.9
Nocturnal*	118 (60)	340	5.7	56 (56)	184	6.2
Major	3 (2)	4	0.1	1 (1)	1	<0.1
Minor	112 (57)	293	4.9	47 (47)	157	5.3
Symptoms only	25 (13)	33	0.6	19 (19)	23	0.8
Unclassified	6 (3)	10	0.2	1 (1)	3	0.1
Blood glucose ≤36 mg/dL[1]	18 (9)	25	0.4	8 (8)	19	0.6

*Nocturnal = episode between 12 a.m. – 5:59 a.m. (events with missing time are excluded)
[1]post-hoc analysis

Hyperglycemic episodes: Hyperglycemic episodes (plasma glucose >300 mg/dL) that were considered adverse events were recorded in the case report form. Hyperglycemia was reported in 21 (11%) aspart-treated patients and 17 (17%) lispro-treated patients.

Diabetic ketoacidosis: Episodes of diabetic ketoacidosis (DKA) were to be communicated from the patient/caregiver to the investigator throughout the trial. The sponsor pre-specified the criteria for mild, moderate, and severe DKA based on serum pH, serum bicarbonate, and mental status changes using the 2002 American Diabetes Association Clinical Practice Guidelines. There were few reported episodes of DKA (3 events in the aspart group and 2 events in the lispro group). However, 1 of these aspart-treated patients did not have positive serum ketones during testing, making DKA unlikely. The Sponsor also excluded a second aspart-treated patient, because of failure to meet the pre-specified criteria for DKA (presumably because there is no mention in the report of results for urine or serum ketones). Regardless, inclusion or exclusion of this patient does not change the overall conclusions.

Infusion site reactions: The Sponsor classified the following preferred terms as infusion site reactions: catheter site-related reaction and infusion site erythema, induration, inflammation, irritation, pruritus, rash, reaction, swelling, or vesicles. Based on this definition, 34 (17%) aspart-treated patients and 21 (21%) lispro-treated patients reported treatment-emergent infusion site reactions.

Reviewer's comments: The Sponsor did not include the following preferred terms in the definition of infusion site reactions: catheter-related complication (2 cases with aspart vs. 1 case with lispro), catheter site hemorrhage (3 vs. 1), infusion site bruising (1 vs. 1), infusion site hypertrophy (4 vs. 8), infusion site induration (5 vs. 2), infusion site mass (0 vs. 2), infusion site pain (0 vs. 1), infusion site scar (1 vs. 0), injection site nodule (0 vs. 2), and infusion site infection (7 vs. 2).

Device-related issues were reported by 27 (14%) aspart-treated patients and 10 (10%) lispro-treated patients. Most of these issues were related to pump malfunction or kinked/occluded tubing.

7. Laboratory evaluations: There were no clinically meaningful changes from baseline in the mean or median values of the standard laboratory parameters.

None of the patients developed treatment-emergent elevations to more than twice the upper limit of normal for white blood cell count, hematocrit, or platelet count. Only 1 patient had a biochemistry parameter more than 2 times the upper limit of normal. This patient (treated with aspart) had a viral infection during Week 7-8 and had an increase in AST from 12 U/L at baseline to 63 U/L at Week 16 (reference range 8-30 U/L) and had an increase in ALT from 7 U/L at baseline to 36 U/L at Week 16 (reference range 5-25 U/L). Transaminitis is not a known side effect of insulin therapy.

Two aspart-treated patients (1.0%) and 3 lispro-treated patients (3.0%) had eosinophil counts >2 times the upper limit of normal at Week 16, which is most likely related to an underlying allergic state although some of these patients were asymptomatic. All 5 of these patients had elevated eosinophil counts at screening. Two aspart-treated patients had 1% atypical lymphocytes without symptoms at Week 16, which most likely resulted from prior viral infection. There were no other aspart-treated patients with differential counts >2 times the upper limit of normal.

Insulin antibodies: Table 11 summarizes the percent binding of cross-reacting insulin antibodies. The aspart and lispro groups had similar median percent binding of cross-reacting antibodies at baseline (25-27%). There were minimal changes in percent binding at the end of the study that are not expected to be clinically significant.

Table 11. Cross-reacting insulin antibodies (% binding)			
	N	Baseline Median (min-max)	Change from baseline* Median (min-max)
Human insulin + aspart assay			
Aspart	187	26 (1-74)	2 (-17, 58)
Lispro	94	27 (0-76)	-1 (-30, 12)
Human insulin + lispro assay			
Aspart	185	25 (1-73)	1 (-17, 58)
Lispro	93	26 (0-69)	-1 (-29, 12)
*Last observation carried forward			

8. Vital Signs: Neither group had clinically meaningful changes from baseline in blood pressure or heart rate. The mean increase in height from screening to Week 16 was 1.6 cm for the aspart group and 1.7 cm for the lispro group.

Body weight: Over the 16 week treatment period, there was a mean increase in body weight of 1.8 kg with aspart and 1.6 kg with lispro (Table 12). Therefore, the increase in body weight with aspart relative to lispro was 0.2 kg (p=0.39).

Table 12. Change in body weight from baseline				
	N	Baseline weight (kg) mean (SD)	Change in weight (kg) Mean (SD)	Aspart – Lispro Mean (95% confidence interval)
Aspart	196	54.1 (19.7)	1.8 (2.1)	0.2 (-0.3, 0.7); p=0.39
Lispro	99	55.5 (19.0)	1.6 (2.1)	

9. Supportive safety from Study 1507: In this supportive study, 20 patients were assigned in a non-randomized fashion to treatment with aspart via insulin pump. These patients had a mean age of 5.7 years (range 3.3-7.0 years), mean baseline HbA1c of 7.7% (range 6.3-9.1%), and median duration of diabetes of 22 months (range 12-68 months). After 26 weeks of treatment, the mean HbA1c was 7.6%. There were no deaths or withdrawals due to adverse events. Two of these 20 patients reported serious adverse events (one patient with severe hypoglycemia during physical activity 2 hours after an injection of mealtime aspart; a second patient with dehydration, ketonuria, fever, and diarrhea in the setting of acute gastroenterocolitis). Eleven (55%) of these 20 patients reported non-serious adverse events, which were mostly related to upper respiratory tract infections.

Safety labs were only measured at screening.

With regard to hypoglycemia, the insulin pump arm had 1 patient with a major event (compared to 1 patient in each of the other arms) and 17 patients with a

total of 235 minor events (compared to 18-19 patients with 189-242 events in the other arms).

10. Postmarketing data: Joslyn Swann (Office of Surveillance and Epidemiology) reviewed the postmarketing reports of anaphylaxis associated with the use of aspart since FDA approval in 2000. She identified 13 potential cases of anaphylaxis, although aspart was continued in some of these reports. There were 10 other cases of hypersensitivity reactions. Per Dr. Zawadzki, there were at least 3 reports that likely represent anaphylaxis associated with the use of aspart. Based on these analyses, I agree with Dr. Zawadzki that the term "anaphylaxis" should be included in the label under Warnings and Precautions.

11. Safety Conclusions (apply to Study 2181 unless noted otherwise):

Deaths and withdrawals: There were no deaths, and only 1 withdrawal due to an adverse event (a lispro-treated patient requested to be discontinued after having persistent hyperglycemia due to repeated infusion set occlusions).

Serious adverse events: Treatment-emergent serious adverse events were reported in 5 (2.5%) aspart-treated patients (2 with hypoglycemia, two with hyperglycemia or diabetic ketoacidosis, and 1 with skin laceration caused by an injury from glass) and in 1 (1%) lispro-treated patient (hypoglycemia).

Common adverse events: The following common adverse events (incidence ≥5% in the aspart group) occurred more frequently with aspart than with lispro: Nasopharyngitis (10.1% vs. 10.0%), headache (8.1% vs. 8.0%), pyrexia (6.1% vs. 4.0%), nausea (5.1% vs. 2.0%), and otitis media (5.1% vs. 2.0%).

Hypoglycemia: Most of the aspart and lispro-treated patients reported hypoglycemia, although the majority of the events were minor episodes that were self-treated. Approximately 10% of patients in both groups had at least 1 major episode of hypoglycemia (severe central nervous system symptoms consistent with hypoglycemia requiring assistance from another party).

Hyperglycemia and diabetic ketoacidosis: Hyperglycemia (plasma glucose >300 mg/dL) was reported in 21 (10.6%) aspart-treated patients and 17 (17%) lispro-treated patients. There were few reported episodes of possible diabetic ketoacidosis (3 in the aspart group and 2 in the lispro group).

Infusion site reactions and device-related issues: A total of 34 (17.3%) aspart-treated patients and 21 (21.2%) lispro-treated patients reported selected infusion site reactions. Device-related issues were reported by 27 (14%) aspart-treated patients and 10 (10%) lispro-treated patients. Most of these device issues were related to pump malfunction or kinked/occluded tubing.

Laboratory evaluations: There were no clinically meaningful changes from baseline in the mean or median values of the standard laboratory parameters. None of the patients developed treatment-emergent elevations to more than twice the upper limit of normal for white blood cell count, hematocrit, or platelet count. Only 1 patient had a biochemistry parameter more than 2 times the upper limit of normal (increase in AST from 12 U/L to 63 U/L at Week 16). Transaminitis is not a known side effect of insulin therapy.

Insulin antibodies: The aspart and lispro groups had similar median values for percent binding of cross-reacting antibodies at baseline (25-27%). There were minimal changes in percent binding at the end of the study that are not expected to be clinically significant.

Vital Signs: The mean increase in height from screening to Week 16 was 1.6 cm for the aspart group and 1.7 cm for the lispro group. Over the 16 week treatment period, there was a mean increase in body weight of 1.8 kg with aspart and 1.6 kg with lispro. Therefore, the increase in body weight with aspart relative to lispro was 0.2 kg (p=0.39).

Study 1507: The limited supportive findings from Study 1507 did not identify additional safety concerns with pump use of aspart in children.

Postmarketing data: There are several postmarketing reports of anaphylaxis.

IV. PHARMACOLOGY/TOXICOLOGY

This supplement does not contain new non-clinical toxicology data.

V. CLINICAL PHARMACOLOGY

This supplement does not contain new clinical pharmacology data.

VI. CHEMISTRY, MANUFACTURING, AND CONTROLS

This supplement does not contain new chemistry data.

VII. OTHER REGULATORY REQUIREMENTS

1. Financial Disclosure: Dr. Zawadzki reviewed the financial disclosures of the clinical investigators and did not detect any potential financial conflicts of interest.

2. Pediatrics: This submission adequately fulfills the Sponsor's postmarketing commitment under PREA for an insulin pump study of aspart in children and adolescents with type 1 diabetes.

Dr. Zawadzki is recommending that we waive the requirement for a pediatric study of intravenous aspart when we take an approval action on the current supplement, stating that there is no physiologic reason to suspect intravenous insulin would act differently in the pediatric population.

(b) (4) pediatric study for intravenous glulisine (another fast-acting insulin analog) and recently (b) (4) . (b) (4) . A consistent approach across products should be taken with regard to (b) (4) for the intravenous use of insulin analogs.

3. Clinical audits and inspections: FDA did not inspect any clinical sites.

VIII. CONCLUSIONS AND RECOMMENDATIONS

1. Conclusions: This was a randomized, open-label, active-controlled, non-inferiority trial that compared 16 weeks of aspart to lispro in children and adolescents (4-18 years old) with type 1 diabetes using insulin pump therapy. The mean baseline HbA1c was 8.0% in the aspart group and 8.2% in the lispro group. The LS mean change in HbA1c from baseline to study end was -0.2% with aspart and -0.1% with lispro. Based on the pre-specified non-inferiority margin of 0.4%, aspart was found to be non-inferior to lispro. Limitations of the trial include the open-label design and relatively short treatment period (16 weeks), although these features are typical of insulin trials in patients with type 1 diabetes. The mean HbA1c and total daily insulin dose at baseline were similar to the corresponding values at study end, suggesting minimal adjustment in insulin doses over the 16 week treatment period. Maintaining the status quo with regard to insulin doses may have biased results towards non-inferiority.

Other pertinent findings include a mean weight gain of 1.6-1.8 kg over the 16 week trial. As expected with all insulin therapies, hypoglycemia was common although most hypoglycemic episodes were minor. The incidence of major hypoglycemia was 10% in both treatment groups, which is higher than that reported in a 16-week insulin pump study of aspart vs. buffered human insulin in adults with type 1 diabetes (2-3%). Children are at a higher risk for hypoglycemia than adults, as reflected by their higher glycemic targets in the American Diabetes Association Clinical Practice Guidelines.

Other expected findings included infusion site reactions and device-related issues (e.g., catheter kinking). Percent binding of cross-reacting insulin

antibodies at study end was essentially unchanged from baseline in both treatment groups.

A review of the Adverse Event Reporting Systems (AERS) identified several likely cases of anaphylaxis associated with aspart.

This trial fulfills the Sponsor's postmarketing requirement under PREA to study aspart in children with type 1 diabetes who are using an insulin pump.

2. Recommendation: APPROVAL (which is in agreement with Dr. Zawadzki's conclusion).

In addition to the efficacy results from Study 2181, the revised label should include the following safety findings for pump therapy with aspart vs. lispro in children with type 1 diabetes:

- Changes in body weight
- Incidence of severe hypoglycemia

In addition, information about the postmarketing reports of anaphylaxis should be included under the Warnings and Precautions section of the label, due to the seriousness of this side effect.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Hylton Joffe
3/14/2008 05:46:27 PM
MEDICAL OFFICER

Mary Parks
3/14/2008 05:52:54 PM
MEDICAL OFFICER
Concur with Dr. Joffe's recommendations.

CLINICAL REVIEW

Application Type	NDA 20-986
Submission Number	047
Submission Code	SE5
Letter Date	May 11, 2007
PDUFA Goal Date	March 14, 2008
Reviewer Name	Joanna K. Zawadzki, M.D.
Review Completion Date	February 26, 2008; revised March 12, 2008
Established Name	Insulin Aspart
Trade Name	NovoLog®,
Therapeutic Class	3031500 (insulin analog)
Applicant	Novo Nordisk, Inc.
Priority Designation	S
Formulation	Injection solution 3.5 mg insulin aspart (100 Units/ml) 10 ml vial for use in external insulin pumps
Dosing Regimen	Dosing is adjusted individually for each patient
Indication	Treatment of Diabetes Mellitus
Intended Population	Pediatric Patients with Type 1 Diabetes who use external insulin pumps
Related IND	IND 48,231
Project Manager	Rachel Hartford; Enid Galliers
Statisticians	Lee Pian, Ph.D., Reviewer J. Todd Sahlroot, Ph.D., Team Leader
Team Leader	Hylton Joffe, M.D.
Division Director	Mary H. Parks, M.D.

Table of Contents

Disclaimer: Many of the tables are cited from the NDA supplement and retain the original table numbers.

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of this efficacy supplement. Specifically, this reviewer recommends approval of the following:

- the pediatric indication of continuous subcutaneous insulin infusion (CSII) by external insulin pump for treatment of hyperglycemia in patients with type 1 diabetes mellitus;
- the prescribing information for NovoLog insulin analog (Insulin Aspart (Asp) [rDNA origin]) in the revised Physician Labeling Rule (PLR) format1, pending agreement with FDA modifications.
- a waiver for children ages three and younger, as there are inadequate number of children in this age group for study, and efficacy and safety data are not expected to differ from those observed in older children.

Additional Recommendation Regarding Pediatric Intravenous Administration of NovoLog®

The intravenous indication for NovoLog was based on an adult pharmacokinetic pharmacodynamic study and it was approved on October 21, 2005. The pediatric intravenous indication was not specifically mentioned in the approval letter for the intravenous indication. In fact, that letter stated the following:

"All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application."

Presumably the last sentence referred to the original pediatric subcutaneous indication for aspart, which was approved on September 13, 2004

Recommendation:

This reviewer recommends that we waive the requirement for the pediatric intravenous study. There is no physiologic reason to suspect intravenous insulin would act differently in the pediatric population. Intravenous insulin should be administered in a hospital setting by trained personnel, so the 'in use' aspect that is evaluated in clinical studies should also not differ. This topic was discussed with members of the FDA Pediatric Review Committee. They concurred that the product is already appropriately labeled in the pediatric population and further pediatric

1 21CFR201.57, Revised as of April 1, 2006.

studies for the pediatric indication are not needed. The Pediatric Review Committee has proposed the following language:

All applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. This drug product (NovoLog®) is fully labeled for use in all appropriate pediatric populations. Therefore, no additional pediatric studies are needed at this time.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Other than the modifications in the prescribing information, no other specific risk management activities are recommended.

1.2.2 Required Phase 4 Commitments

No new Phase 4 commitments are requested.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The main focus of this supplemental NDA application is the conversion of the prescribing information into the Physician Labeling Rule (PLR) format. The NovoLog® insulin analog is the first insulin analog in the PLR format. (b) (4)

Insulin aspart (NovoLog® or NovoRapid®, Novo Nordisk) is an analog of human insulin, in which the amino acid proline has been replaced by aspartic acid in the B-chain position 28 so that the insulin molecule is more monomeric, has less of a tendency to form hexamers, and can

be absorbed more rapidly than human insulin after subcutaneous injection. Insulin aspart subcutaneous injection, [rDNA origin] (NDA 20-986) was approved for the control of hyperglycemia in adult patients with type 1 diabetes mellitus on June 7, 2000 and in pediatric patients on September 13, 2005. Insulin aspart was approved for continuous subcutaneous insulin injection (CSII) by external pumps in adult patients with type 1 diabetes on December 21, 2001 (NDA 20-986 Supplement 003). Since April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred2. As a fulfillment of this requirement, Novo Nordisk has submitted data from two pediatric studies in patients with type 1 diabetes who are using external insulin pump therapy.

Novo Nordisk has submitted data from two post-marketing pediatric Phase 3b studies, Study ANA-2181 and Study ANA 1507, which evaluated the use of continuous subcutaneous insulin infusion (CSII) in 298 children ages 3-18 years and 61 children age less than 7 years, respectively, to complete the postmarketing study commitment under the Pediatric Research Equity Act (PREA). Study ANA-2181 was an open label, randomized study that compared CSII therapy with insulin aspart to CSII therapy with another insulin analog, insulin lispro (Humalog®, Eli Lilly). On the basis of this study, Novo Nordisk has proposed the following additional section in the *Clinical Studies* section of the PLR prescribing information:

(b) (4)

Study ANA-1507 was also an open label study, but one-third of the patients were assigned to pump therapy and the remaining two-thirds of patients were randomized to subcutaneous insulin aspart or insulin lispro therapy. Because Study ANA-1507 was not fully randomized, the data from it are considered supportive in the safety analysis.

2 63 *FR* 66632

The submission of an efficacy supplement for this NDA requires the conversion of the prescribing information for insulin aspart to the revised Physician Labeling Rule (PLR) format3, The FDA-revised label is attached to this review. The conversion of the label to the PLR format was the major effort in this NDA supplement review.

1.3.2 Efficacy

The primary efficacy comparison was non-inferiority of CSII of aspart to insulin lispro in HbA_{1c} change from baseline to Week 16 using a margin of 0.4%.

The data for the primary efficacy comparison were reviewed by the FDA statistician, Lee Piang, Ph.D.

Table 2 displays the mean HbA_{1c} at baseline and week 16 and mean HbA_{1c} change from baseline.

Table 2 displays the analysis of covariance (ANCOVA) results in the least squares mean (LSM) in HbA_{1c} changes from baseline to week 16 for the full analysis set (FAS) using last observation carried forward (LOCF) to impute missing data. The upper bound of the 95% confidence interval, 0.07% is less than the 0.4% non-inferiority margin which indicated the pump treatment with insulin aspart is non inferior to insulin lispro in HbA_{1c} change from baseline (Table 2). ANCOVA results from the per protocol (PP) population were similar.

Table 2. Mean change (SD) from baseline in HbA_{1c} (%) at Week 16

(full analysis set, last observation carried forward)

Treatment	N	Baseline	Week 16	Change
aspart	192	8.02 (0.94)	7.88 (0.93)	-0.13 (0.79)
lispro	96	8.14 (0.85)	8.07 (0.85)	-0.08 (0.70)

Table 3. Least squares mean change from baseline in HbA_{1c} (%) at Week 16 – ANCOVA* (LOCF)

Treatment	LSMean	StdErr	Lower CL	Upper CL
aspart	-0.24	0.08	-0.40	-0.07
lispro	-0.13	0.10	-0.33	0.06
Aspart minus lispro	**-0.10**	**(0.09)**	**[-0.27**	**0.07]**

3 21CFR201.57, Revised as of April 1, 2006.

*ANCOVA (analysis of covariance) model included treatment group and age group as fixed effect and Baseline HbA_{1c} as covariate

1.3.3 Safety

Safety assessments in Study ANA-2181 included reports of adverse events and episodes of hypoglycemia, hyperglycemia, and diabetic ketoacidosis; physical examination findings; laboratory test results for hematology, blood chemistry, and insulin antibody binding. No deaths were reported during the clinical studies. No significant differences in rates of hypoglycemia with central nervous system symptoms requiring assistance of a third person were observed between the aspart and lispro treatment groups. No significant differences in rates of diabetic ketoacidosis or infusion site reactions were observed. Data observed in the pediatric pump studies were similar to data observed in adult pump studies.

1.3.4 Dosing Regimen and Administration

Insulin doses, including those of insulin analogs such as aspart (NovoLog®), must be individualized – whether administered by multiple subcutaneous doses or by continuous subcutaneous insulin infusion.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Insulin aspart (NovoLog® or NovoRapid®, Novo Nordisk) is an analog of human insulin, in which the amino acid proline has been replaced by aspartic acid in the B-chain position 28 so that the insulin molecule is more monomeric, has less of a tendency to form hexamers, and can be absorbed more rapidly than human insulin after subcutaneous injection. Insulin aspart injection, [rDNA origin]) (NDA 20-986) was approved for the control of hyperglycemia in adult patients with type 1 diabetes mellitus on June 7, 2000 and in pediatric patients on September 13, 2005. Insulin aspart was approved for continuous subcutaneous insulin injection (CSII) by external pumps in adult patients with type 1 diabetes on December 21, 2001 (NDA 20-986 Supplement 003). Since April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred4. As a fulfillment of this requirement, Novo Nordisk has submitted data from two pediatric studies in patients with type 1 diabetes who are using external insulin pump therapy. Insulin aspart has also been approved for intravenous use in October 21, 2005 (NDA 20-986 Supplement 032).

2.2 Currently Available Treatment for Indications

Currently available recombinant DNA human insulins and insulin analogs are available for the treatment of type 1 and type 2 diabetes mellitus and gestational diabetes. Animal-derived (beef and/or pork) insulins are no longer marketed. A list of types of human insulins and insulin analogs and adult and pediatric indications are included in the table below. Of note, insulin lispro has been approved for adult continuous subcutaneous insulin infusion (CSII) pump therapy but not specifically for pediatric continuous subcutaneous insulin infusion (CSII) pump therapy.

4 63 *FR* 66632 http://www.fda.gov/ohrms/dockets/98fr/042401a.htm accessed February 26, 2008.

Table 4. Approval of Insulins and Insulin Analogs for Adult and Pediatric Use5

Insulin Product	Indications	Adult Approval	Pediatric Approval
Aspart (NovoLog, NovoNordisk)	• subcutaneous • continuous subcutaneous insulin infusion • intravenous	6/7/2000 12/21/01 10/21/05	9/13/05 Pending this review Recommend waiver
Detemir (Levemir, NovoNordisk)	• subcutaneous	6/16/2005	?date
Glargine (Lantus, Sanofi Aventis US)	• subcutaneous	4/20/2000	?date
Glulisine (Apidra, Sanofi Aventis US)	• subcutaneous • continuous subcutaneous insulin infusion • intravenous	4/16/04 4/16/04 4/12/07	Not approved
Lispro (Humalog, Lilly)	• subcutaneous • continuous subcutaneous insulin infusion	6/14/1996 6/2/04	4/4/00
Human recombinant insulin (Humulin R and N, Lilly)	• subcutaneous	10/28/1982	
Human recombinant insulin (Novolin R, Novo Nordisk)	• subcutaneous	6/25/1991	
Human recombinant insulin (Novolin N, Novo Nordisk)	• subcutaneous	7/1/1991	
Human recombinant (Exubera, Pfizer)	• inhaled	1/27/2006	Not approved

5 Drugs@FDA. The most recent available labeling information is cited; accessed 11/28/06

2.3 Availability of Proposed Active Ingredient in the United States

Insulin aspart is available in the United States.

2.4 Presubmission Regulatory Activity

Novo Nordisk had submitted a pediatric plan for the use of the insulin analog NovoLog® (aspart) in external insulin pumps (5/06/02) and a revised pediatric plan (8/18/03). The applicant had initially proposed a 16-week study in 94 children ages 6-17 with DM1 and at least 3-month use of a pump in a 3:2 randomization to aspart and lispro (Humalog). The primary FDA recommendation was the use of buffered human insulin as a control, as lispro has not been approved for pump use. A 3-arm trial was suggested as an option. The sponsor stated that buffered human insulin was not an appropriate control, as rapid acting insulin analogs were the standard of care in children and adolescents, including in external insulin pump therapy.

The applicant submitted a revised draft synopsis, which incorporated the FDA recommendations (other than the selection of the comparator), for an open-label, randomized 16-week study in 250 children (ages 2-18) with type 1 diabetes mellitus and HbA1c < 12% and at least 3 months of prior pump therapy to be randomized 1:1 to external insulin pump therapy with aspart or lispro. The primary objective was to demonstrate the non-inferiority of aspart treatment to lispro, as measured by HbA1c. The non-inferiority margin of 0.4% in HbA1c change, 80% power, 1-side alpha level of 0.025, and a drop-out rate of 20% were used to calculate the sample size.

Novo Nordisk had announced the discontinuation of Velosulin® BR buffered regular human insulin, effective approximately 4/30/04. This was the only marketed buffered regular human insulin. At that time, Velosulin buffered insulin and NovoLog® (aspart) were the only insulin products approved for pump use. Humalog® (lispro) was approved for pump use on June 2, 2004.

The main FDA concern was the use of lispro insulin analog as the comparator, as lispro had not yet been approved for use in external insulin pump therapy. Most patients with Type 1 diabetes mellitus were using the rapid acting insulin analogs. However, FDA had sent comments to the applicant indicating that approval of NovoLog insulin for pump therapy in the pediatric population should be based on a comparison to an approved insulin for pump use. Velosulin® buffered insulin was the only other insulin approved for pump therapy, and this study would be the first pediatric study. The planned discontinuation of manufacture of Velosulin buffered insulin, which was recommended as a comparator in a 2-arm or 3-arm design, complicated this recommendation. FDA noted that "Though a comparison between aspart and lispro may provide clinical information, it is unlikely that such a study would result in a claim." in a comment sent to Novo Nordisk on December 19, 2003.

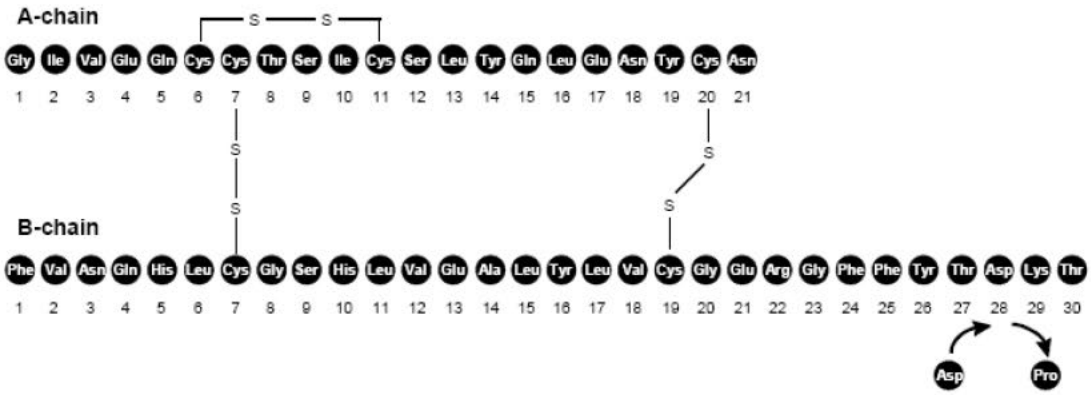
In vitro studies submitted [redacted] (b) (4) resulted in a significant under delivery of insulin on day one with the MiniMed pumps (b) (4) Thus a comparison to lispro in the MiniMed pump could cause a potential bias, as there would be lower rates of hypoglycemia and lower efficacy. Good glycemic control would be expected three months after external pump therapy initiation; maintenance of good glycemic control would be expected during the 16-week study.

Novo Nordisk did not initiate Study ANA-2181 until lispro (Humalog®) had been approved for continuous subcutaneous insulin infusion by external pump in the adult type 1 diabetes population (6/2/04). Of note, Velosulin BR (buffered insulin recombinant human insulin) was approved July 19, 1999 for use in external pumps in a study of 20 patients with type 1 diabetes ages 24-55. No insulin or insulin analog has been previously approved for use in pediatric patients with type 1 diabetes using continuous subcutaneous insulin infusion pump therapy.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Insulin aspart (NovoLog®, Novo Nordisk) is an analog of human insulin, in which the amino acid proline has been replaced by aspartic acid in the B-chain position 28. It is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae* (baker's yeast) as the production organism. Insulin aspart has the empirical formula $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8. The structural formula is indicated below:



No new chemistry data were submitted in this supplement.

(b) (4) [redacted]

3.2 Animal Pharmacology/Toxicology

No new toxicology data were submitted in this supplement.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This efficacy supplement was submitted electronically to the Electronic Document Room (EDR). The submissions were accessed at the following addresses:

\\CDSESUB1\N20986\S_047\2007-05-11

\\CDSESUB1\N20986\S_047\2007-08-08 patent info

\\CDSESUB1\N20986\S_047\2007-08-29 labeling

\\CDSESUB1\NONECTD\3166888 requested tables submitted 101007 SE5 BZ

\\CDSESUB1\NONECTD\3863910 proposed PLR submitted 111207 SE5 BL

\\CDSESUB1\EVSPROD\NDA020986\0000 submitted 011608

\\Cdsesub1\evsprod\NDA020986\0003\m1\us proposed/revised labeling - response to FDA labeling

4.2 Tables of Clinical Studies

Table 1–1 Trial Characteristics–Insulin Aspart Paediatric CSII Trials

Trial ID	Design	Treatment	Primary Endpoint	Subjects
Pivotal Trial in Children and Adolescents (3 to 18 Years of Age)				
ANA-2181	OL, randomised (2:1), parallel-group, active-control, multi-centre study (45 sites in the US). Study duration: 16 wks	• Insulin aspart CSII • Insulin lispro CSII	HbA_{1c} change from baseline at Wk 16	298 children and adolescents (3-18 years [youngest subject enrolled was 4 years]) with T1D ≥ 1 yr, HbA_{1c} ≤ 10% and treated continuously for the previous 3 months with insulin aspart or insulin lispro CSII.
Supportive Trial in Children (< 7 Years of Age)				
ANA-1507	OL, 3-arm (2 arms 1:1 randomised, 1 arm fixed allocation [insulin aspart CSII]), parallel-group, multi-centre (5 sites in Poland) study. Study duration: 29 wks total (3-wk run-in, 26 wk treatment)	• Insulin aspart CSII • Insulin aspart MIT (+ basal NPH) • Regular HI MIT (+ basal NPH)	HbA_{1c} 26 wks after randomisation	61 children < 7 yrs with T1D, HbA_{1c} < 12%, on > 2 injections/day of regular HI and NPH insulin (MIT).

OL = open-label; CSII = continuous subcutaneous insulin infusion; MIT = multiple injection therapy; T1D = type 1 diabetes; HI = human insulin.

4.3 Review Strategy

The submitted study reports were reviewed. The FDA statistician confirmed the primary efficacy data for Study ANA-2181. The major effort in this review was the conversion of the prescribing information into the Physician Labeling Rule (PLR) format. For more details about the labeling review strategy, please see Section 9.4 Labeling Review.

4.4 Data Quality and Integrity

Data quality and integrity appeared adequate. No site inspections were conducted for this NDA supplement.

4.5 Compliance with Good Clinical Practices

The study appeared to comply with good clinical practices.

4.6 Financial Disclosures

In compliance with the Final Rule on Financial Disclosure by Clinical Investigators (published 2/2/98 (63 FR 5233; revised 12/31/98 (63 FR 72171), the financial certification disclosure, OMB Form No. 0910-0396, is signed by Anders Desgaard, and paragraph (1) is checked, certifying that there were no financial agreements between the sponsor and the investigators where compensation was linked to study outcome (as defined in 21 CFR 54.2(a), and that no clinical investigator reported any proprietary interest in this product or significant equity in the sponsor (as defined in 21 CFR 54.2(b), or the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f). The Novo Nordisk certifications signed by the individual investigators specified that the total payment (including research grants, equipment donations, retainers, honoraria, etc.) to each investigator or institution would not exceed $25,000, exclusive of the cost of conducting the clinical trial.

5 CLINICAL PHARMACOLOGY

No new clinical pharmacology studies with insulin aspart have been submitted with this NDA supplement.

6 INTEGRATED REVIEW OF EFFICACY

Study titles:

Study ANA-2181
"External Continuous Subcutaneous Infusion of Insulin Aspart (NovoLog) versus Insulin Lispro (Humalog): An Open-Label, Randomised, Parallel Group, Multicentre Study in Children and Adolescents with Type 1 Diabetes"

Study ANA-1507
"A multicentre open label 29 weeks three armed efficacy and safety study with two arms randomised and one arm with fixed allocation to CSII comparing insulin NovoRapid multiple injection or CSII with Actrapid multiple injection in diabetes type 1 children below 7 years of age"

Study ANA-2181 is the major study discussed in this review. The other study, **Study ANA-1507**, was not randomized and the efficacy data are described briefly. Study ANA-1507 was an open label study, but one-third of the patients were assigned to pump therapy and the remaining two-thirds of patients were randomized to subcutaneous insulin aspart or insulin lispro therapy. The data from Study ANA-1507 were reviewed primarily as supportive safety data. The studies are summarized in the sponsor's table below.

Table 1–1 Trial Characteristics–Insulin Aspart Paediatric CSII Trials

Trial ID	Design	Treatment	Primary Endpoint	Subjects
Pivotal Trial in Children and Adolescents (3 to 18 Years of Age)				
ANA-2181	OL, randomised (2:1), parallel-group, active-control, multi-centre study (45 sites in the US). Study duration: 16 wks	• Insulin aspart CSII • Insulin lispro CSII	HbA_{1c} change from baseline at Wk 16	298 children and adolescents (3-18 years [youngest subject enrolled was 4 years]) with T1D ≥ 1 yr, HbA_{1c} ≤ 10% and treated continuously for the previous 3 months with insulin aspart or insulin lispro CSII.
Supportive Trial in Children (< 7 Years of Age)				
ANA-1507	OL, 3-arm (2 arms 1:1 randomised, 1 arm fixed allocation [insulin aspart CSII]), parallel-group, multi-centre (5 sites in Poland) study. Study duration: 29 wks total (3-wk run-in, 26 wk treatment)	• Insulin aspart CSII • Insulin aspart MIT (+ basal NPH) • Regular HI MIT (+ basal NPH)	HbA_{1c} 26 wks after randomisation	61 children < 7 yrs with T1D, HbA_{1c} < 12%, on > 2 injections/day of regular HI and NPH insulin (MIT).

OL = open-label; CSII = continuous subcutaneous insulin infusion; MIT = multiple injection therapy; T1D = type 1 diabetes; HI = human insulin.

6.1 Indication

Treatment of type 1 diabetes mellitus in children and adolescents with continuous subcutaneous insulin infusion (CSII) by external pump.

6.2 Methods

6.2.1 General Discussion of Endpoints

Primary Objective of Study ANA-2181:
To demonstrate non-inferiority, as measured by HbA1c after 16 weeks of continuous external infusion (CSII) of aspart in comparison with insulin lispro in children and adolescents with type 1 diabetes

Efficacy endpoint

HbA1c change from baseline after 16 weeks of treatment was the primary efficacy endpoint in the non-inferiority analysis. Secondary efficacy assessments included self-monitoring of blood glucose (SMBG) measurements, fasting plasma glucose, and fasting lipid parameters.

Secondary Objectives:

Efficacy

- Glucose variability as determined by subject's self glucose monitoring
- Four-point self-monitored blood glucose (SMBG) daily (results were captured for the two days prior to each office visit.)
- Percentage of subjects with HbA1c < 7.0% and ≤6.5 %
- Fasting plasma glucose (FPG)
- Fasting lipid profile

Safety

- Incidence and frequency of hypoglycemia (blood glucose (BG) ≤56 mg/dL or 3.1 mmol/L)
- Incidence of diabetic ketoacidosis (DKA)
- Incidence and frequency of hyperglycemia (BG > 300 mg/dL or 16.6 mmol/L)
- Clinical evaluations (physical examination and vital signs)
- Urine screen and laboratory tests (haematology and chemistry)
- Change in fundoscopy from baseline (this information was not collected in the CRFs or analysed.)
- Change in insulin antibodies from baseline
- Adverse events

Other

- Total daily insulin requirements
- Local infusion site reactions
- Infusion set duration (this information was not collected in the CRFs or analysed)

6.2.2 Study Design of **Study ANA-2181**

Study design *(p 20 of study report)*

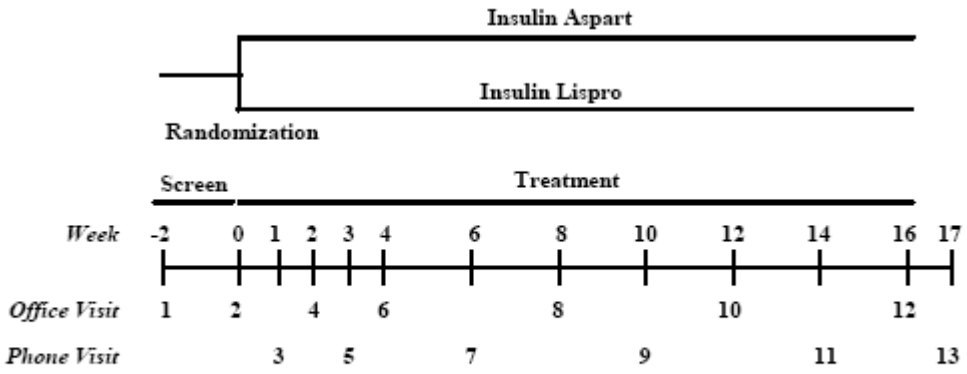


Figure 9–1 Trial Diagram

Timing of assessments:

Office Visits: Screening (-2 weeks), Baseline, Week 2, Week 4 , Week 8, Week 12,Week 16
Phone Visits: Week 1, Week 3, Week 6, Week 10, Week 14, Week 17.

Children and adolescents with type 1 diabetes were randomized in a (2:1) manner to receive either aspart or insulin lispro as a continuous subcutaneous insulin infusion (CSII) in an external pump with changes in reservoir, infusion set, and infusion site at least once every 48 hours. Subjects were stratified by age (3 to 5 years, 6 to 11 years, and 12 to 18 years). This clinical trial was designed to test the non-inferiority of aspart compared with lispro for paediatric use in CSII pumps. This was designed as a multicenter study in order to observe the effect of aspart or lispro in a range of US clinical settings and in order to recruit sufficient subjects. At Visit 2, randomization was carried out centrally using a telephone randomization system (Interactive Voice Response System [IVRS]).

Treatments

Insulin aspart or insulin lispro was administered via continuous subcutaneous infusion using the patients' own insulin pump. The following pumps were considered acceptable:

- MiniMed series 511, 512, 515, 712 , 715 pumps (Medtronic Diabetes, Northridge, CA)
- Animas 1000 series pumps: IR1000, IR1200 and IR1250 (Animas Corporation, West Chester, PA)
- Deltec Cozmo pump (Smiths Medical MD, St. Paul, MN)

Pump supplies, including infusion sets and reservoirs, glucose meters, test strips, and topical anesthetic cream, were provided to the patients. The specific basal and pre-mealtime bolus doses

for each patient were 'determined at the Investigator's discretion" to achieve the pre-specified glycemic targets. The glycemic targets were provided in Appendix D of the Study Protocol and are cited below.

Glycemic Targets			
	Plasma BG Range (mg/dL)		
Time	**Ages 3-5**	**Ages 6 – 11**	**Ages 12 - 18**
Preprandial	80-180	80 – 180	80 – 150
2hrPP	<180	< 180	<160
hs	120-180	120 – 180	110 –160

Insulin adjustments were aided by daily self-monitoring of blood glucose (SMBG) profiles (minimum four times daily) and 8-point profiles. Infusion insertion sites included the abdomen, lower back, hips, and thighs. In fusion sites and reservoirs were to be changed every 48 hours.

Study population

The entry criteria are summarized below.

Entry Criteria

- Pediatric patients (ages 3-18) with type 1 diabetes mellitus of at lest one-year duration and treated continuously with continuous subcutaneous insulin infusion(CSII) pump therapy with lispro or aspart for the previous 3 months;
- Current CSII insulin analog basal rate > 0.05 units per hour
- HbA1c ≤ 10%
- Absence of active proliferative retinopathy, serum creatinine elevation, recurrent severe hypoglycemia, hypoglycemia unawareness, abnormal thyroid function, pregnancy, lactation or failure to use approved contraceptive measure in sexually active females of child bearing potential, chronic use of steroids in adrenal-suppressive doses
- Parental or guardian consent and ability and willingness to record self-monitoring of glucose and continue CSII pump therapy with child

The inclusion and exclusion criteria cited by the sponsor are quoted below.

Inclusion Criteria

- The subject's parent/legal guardian gave signed informed consent including HIPAA requirements and child assent (if applicable) before beginning any trial-related activities. Trial related activities were defined as any procedures that would not have been

performed during normal management of the subject. Subjects who were 18 years of age signed the Informed Consent Form and did not require parental consent.

- Pediatric subjects (ages 3-18) diagnosed with type 1 diabetes for a duration of at least 1 year; and treated continuously for the previous 3 months with CSII therapy using either aspart or lispro.
- HbA1c ≤10% (one retest within 1 week was permitted)
- Subjects had to be using one the following pumps: MiniMed® 511, 512, 515, 712, 715; Animas 1000 series pumps by Animas Corporation (IR1000, IR1200 and IR1250 pumps), the Deltec Cozmo® pump by Smiths Medical MD, Inc.
- Subject, parent/guardian willing to continue CSII for 16 weeks and accept the randomized insulin assigned.
- Subject, parent/guardian willing and able to perform and record in the subject's diary the SMBG profile at least 4 times daily.
- Subject, parent/guardian willing and able to perform and record in the subject's diary the SMBG profile at least 8 times daily for two days within 72 hours prior to Visit 2 (Week 0) and Visit 12 (Week 16).
- Parent/guardian willing and able to observe (when appropriate) subject performing SMBG and changing reservoirs and inserting infusion sets.

Exclusion criteria

- Chronic use of steroids in adrenal-suppressive doses. Stable doses of inhaled steroids prior to screening were permitted at the discretion of the Medical Monitor (Principal Investigator, or Sub-Principal Investigator) and were approved prior to entry. The use of topical steroids was acceptable.
- History of active proliferative retinopathy
- Subjects with a current basal rate ≤0.05 units per hour.
- Subjects on diluted insulin
- Basal dose was not stable for two weeks prior to screening visit
- Impaired hepatic function (alanine aminotransferase [ALT] > 2.0 times the upper reference limit for age and gender [one retest within one week was permitted])
- Impaired renal function (serum creatinine > the upper reference limit for age [one retest within one week was permitted])
- Abnormal thyroid function (thyroid stimulating hormone [TSH] > 2.0 times the upper reference limit for age and gender [one retest within one week was permitted]).
- Known or suspected allergy to insulin or any component of the study drug
- Recurrent severe hypoglycemia or hypoglycemic unawareness, as judged by the Investigator
- Mental incapacity, unwillingness to follow all study procedures, or language barriers precluding adequate understanding or cooperation
- Any condition that either the Investigator or Sponsor felt would interfere with study participation or evaluation of the results

- Pregnancy, lactation, or failure to use an approved contraceptive measure in sexually-active females of child bearing potential
- The receipt of any investigational drug within one month prior to the trial
- Previous participation in the randomization phase of this trial
- Subjects/caregivers had been unsuccessful in the past 3 months with using CSII and in changing reservoir and infusion sets.

Withdrawal criteria

- Pregnancy or intention of becoming pregnant
- Breastfeeding
- Withdrawal of consent
- An unexplained episode of DKA in the opinion of the Investigator
- Frequent unexplained episodes of minor hypoglycemia, defined by a plasma glucose ≤56 mg/dL or 3.1 mmol/L or symptomatic hypoglycemia with no recorded plasma glucose
- More than one episode of unexplained severe hypoglycemia, defined by a plasma glucose ≤56 mg/dL or 3.1 mmol/L requiring assistance by a 3rd party
- Failure to perform 4-point SMBG profiles or 8-point SMBG profiles per specifications in the protocol
- Failure to accurately record all hypoglycemic or hyperglycemic episodes
- Initiation of concomitant medication that influences glucose homeostasis, e.g., chronic use of steroids in adrenal suppressive doses
- Non-compliance with any of the study procedures
- Failure to dose insulin based on Investigator's and/or site staff's recommendations

Statistics

The Sponsor estimated that 156 patients with type 1 diabetes receiving insulin aspart and 78 patients receiving insulin lispro (2:1 ratio) as a continuous subcutaneous insulin infusion (CSII) in an external pump will have 80% power to establish non-inferiority of insulin aspart vs. insulin lispro in HbA_{1c} change from baseline to week 16 using a non-inferiority margin of 0.4% and assuming a standard deviation of 1.025%. The sponsor planned to enroll 282 patients to account for an estimated drop-out rate of 17%.

To show insulin aspart used in CSII pumps is non-inferior to lispro use in CSII pumps in HbA_{1c} change from baseline after 16 weeks of treatment, the primary analysis is analysis of covariance (ANCOVA) with treatment and age groups (3 to 5, 6 to 11 and 12 to 18 years old) as fixed effects and baseline HbA_{1c} as a covariate. The non-inferiority margin is 0.4%. The intent-to-treat (ITT) population using the last observation carried forward (LOCF) method was used for the primary analysis population.

Demographics

The baseline demographics were similar for the two treatment groups and are summarized in the table below;

Table 11–1 Demographics – All Randomised Subjects

	Aspart	Lispro	All
Number of Subjects	198	100	298
Sex (n (%))			
Male	95 (48.0%)	48 (48.0%)	143 (48.0%)
Female	103 (52.0%)	52 (52.0%)	155 (52.0%)
Race (n (%))			
White	180 (90.9%)	94 (94.0%)	274 (91.9%)
Hispanic	11 (5.6%)	3 (3.0%)	14 (4.7%)
Non-Hispanic	169 (85.4%)	91 (91.0%)	260 (87.2%)
Black	11 (5.6%)	2 (2.0%)	13 (4.4%)
Non-Hispanic	11 (5.6%)	2 (2.0%)	13 (4.4%)
Asian/Pacific Islander	1 (0.5%)	1 (1.0%)	2 (0.7%)
Non-Hispanic	1 (0.5%)	1 (1.0%)	2 (0.7%)
Other	6 (3.0%)	3 (3.0%)	9 (3.0%)
Hispanic	3 (1.5%)	3 (3.0%)	6 (2.0%)
Non-Hispanic	3 (1.5%)	0 (0.0%)	3 (1.0%)
Ethinicity (n (%))			
Hispanic	14 (7.1%)	6 (6.0%)	20 (6.7%)
Non-Hispanic	184 (92.9%)	94 (94.0%)	278 (93.3%)
Age (yrs)			
n	198	100	298
Mean	13.0	13.1	13.0
SD	3.30	3.02	3.21
Median	13.5	13.6	13.6
Min	4.2	4.7	4.2
Max	18.7	18.8	18.8

n = number of subjects.
Cross reference EOT Table 14.2.1.

The baseline metabolic information and diabetes history were also similar for the two treatment groups:

Table 11–2 Baseline Prognostic Information – All Randomised Subjects

	Aspart	Lispro	All
Number of Subjects	198	100	298
Weight (kg)			
n	198	100	298
Mean	54.3	55.8	54.8
SD	19.89	19.13	19.62
Height (m)			
n	198	100	298
Mean	1.6	1.6	1.6
SD	0.18	0.17	0.18
BMI ($kg/(m^2)$)			
n	198	100	298
Mean	21.7	21.8	21.7
SD	4.35	4.37	4.35
FPG (mg/dL)			
n	197	98	295
Mean	170.7	176.1	172.5
SD	77.80	67.47	74.46
HbA_{1c} (%)			
n	198	100	298
Mean	8.0	8.1	8.1
SD	0.94	0.84	0.91

BMI = body-mass index; FPG = fasting plasma glucose.
Cross reference EOT Table 14.2.2.

Table 11–3 Diabetic History – All Randomised Subjects

	Aspart	Lispro	All
Number of Subjects	198	100	298
Diabetes History[a] (yrs)			
Mean	6.1	6.0	6.1
SD	3.36	2.80	3.18
Current Diabetes Therapy (n (%))			
Aspart	87 (43.9%)	44 (44.0%)	131 (44.0%)
Lispro	111 (56.1%)	56 (56.0%)	167 (56.0%)
Type of Insulin Pump (n (%))			
MiniMed 511	52 (26.3%)	26 (26.0%)	78 (26.2%)
MiniMed 512	59 (29.8%)	36 (36.0%)	95 (31.9%)
MiniMed 712	43 (21.7%)	17 (17.0%)	60 (20.1%)
Other	44 (22.2%)	21 (21.0%)	65 (21.8%)
Use of CSII[b] (weeks)			
Mean	121.3	132.7	125.2
SD	80.28	69.99	77.05
Average Total Daily Insulin Dose Before Randomisation (Units)			
Mean	49.5	52.8	50.6
SD	24.17	24.01	24.13
Average Adjusted Total Daily Insulin Dose Before Randomisation (Units/kg)			
Mean	0.89	0.93	0.91
SD	0.259	0.246	0.254

[a.] Diabetic History is calculated from date diabetes was diagnosed to the screening date.
[b.] From the start of CSII to screening date.
Cross reference EOT Table 14.2.3.

6.2.3 Efficacy Findings

The primary efficacy comparison was non-inferiority of CSII of aspart to insulin lispro in HbA_{1c} change from baseline to Week 16 using a margin of 0.4%.

The data for the primary efficacy comparison were reviewed by the FDA statistician, Lee Piang, Ph.D.

Table 2 displays the mean HbA_{1c} at baseline and week 16 and mean HbA_{1c} change from baseline.

Table 3 displays the analysis of covariance (ANCOVA) results in the least squares mean (LSM) in HbA_{1c} changes from baseline to week 16 for the full analysis set (FAS) using last observation carried forward (LOCF) to impute missing data. The upper confidence interval, 0.07% is less than the 0.4% non-inferiority margin which indicated the pump treatment with insulin aspart is non inferior to insulin lispro in HbA_{1c} change from baseline (Table 2). ANCOVA results from the per protocol (PP) population were similar.

Figure 1 displays the HbA_{1c} values by visit using PP population.

Table 2. Mean change (SD) from baseline in HbA_{1c} (%) at Week 16

full analysis set, last observation carried forward

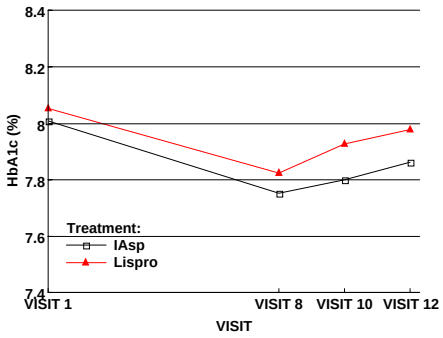
Treatment	N	Baseline	Week 16	Change
aspart	192	8.02 (0.94)	7.88 (0.93)	-0.13 (0.79)
lispro	96	8.14 (0.85)	8.07 (0.85)	-0.08 (0.70)

Table 3. Least squared mean change from baseline in HbA_{1c} (%) at Week 16 – ANCOVA* (LOCF)

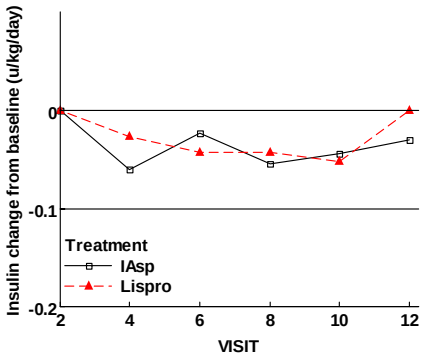
Treatment	LSMean	StdErr	Lower CL	Upper CL
aspart	-0.24	0.08	-0.40	-0.07
lispro	-0.13	0.10	-0.33	0.06
Aspart minus lispro	**-0.10**	**(0.09)**	**[-0.27**	**0.07]**

*ANCOVA (analysis of covariance) model included treatment group and age group as fixed effect and Baseline HbA_{1c} as covariate

Figure 1 Mean HbA_{1c} (%) by visit – Completers



The deterioration of glycemic control after the greatest decline in HbA1c at visit 8 or 8 weeks is frequently observed in clinical trials of diabetes mellitus. Both treatment groups showed similar deterioration.



The applicant also analyzed the HbA1c data by age subgroups (ages 3-5, ages 6-11, and ages 12-18 years). Only ten patients participated in the youngest subgroup, and the remaining patients were distributed between the two other age groups. No significant differences were observed in the two older age groups or in the different treatments (aspart vs. lispro).

Daily Insulin Dose

The total daily insulin doses were not statistically significantly different in the two treatment groups, as indicated in the table below.

Table 11–23 Daily Insulin Dose (U)[a] at Each Visit – ITT Population

	Aspart			Lispro			
Week	n	Mean	SD	n	Mean	SD	p-Value[b]
0	197	49.3	24.15	99	52.7	24.07	0.532
2	192	47.5	22.42	99	51.8	22.76	0.244
4	190	48.6	25.52	98	51.3	23.51	0.793
8	186	47.0	22.51	97	52.4	24.07	0.128
12	186	48.6	24.13	93	50.6	22.57	0.996
16	187	49.4	24.58	92	54.4	25.29	0.225

n = number of subjects.
[a] 2-day average.
[b] p-value is based on the model: average daily insulin dose (U) = treatment.
Cross references: EOT Table 14.3.1.1. and EOT Table 14.3.2.1.

Statistical differences were observed when the insulin dose was adjusted for weight. The applicant notes that "*aspart-treated subjects had a significantly lower mean daily adjusted insulin dose than lispro-treated subjects at Week 8 (p = 0.039) and Week 16 (p = 0.018). Despite a lower adjusted daily insulin dose, aspart-treated subjects had greater reductions in mean*

HbA1c (%) change from baseline at Weeks 8 and 16 than lispro-treated subjects (-0.26% vs. -0.22% at Week 8, -0.13% vs. -0.07% at Week 16, aspart vs lispro respectively).” Given the large standard deviations of the daily doses, the differences in adjusted insulin doses are not likely to be clinically significant.

Table 11–24 Adjusted Insulin Dose (U/kg)[a] at Each Visit – ITT Population

	Aspart			Lispro			
Week	n	Mean	SD	n	Mean	SD	p-Value[b]
0	197	0.89	0.259	99	0.93	0.247	0.344
2	192	0.84	0.230	99	0.91	0.226	0.031*
4	188	0.86	0.251	98	0.90	0.247	0.620
8	185	0.84	0.224	97	0.90	0.219	0.039*
12	186	0.85	0.227	93	0.89	0.200	0.424
16	187	0.86	0.237	92	0.94	0.233	0.018*

n = number of subjects.
[a] Two-day average.
[b] p-value is based on the model adjusted daily insulin dose (U) = treatment.
* Statistically significant difference ($p < 0.05$) aspart vs. lispro.
Cross references: EOT Table 14.3.1.2, EOT Table 14.3.2.2.

6.2.4 Efficacy Conclusion

This reviewer agrees with the applicant that treatment of children and adolescents with type 1 diabetes mellitus with continuous subcutaneous insulin infusion (CSII) by external pump appears to be similar whether insulin aspart or insulin lispro is used. The major limitation of this study, from a regulatory perspective, is the absence of an approved comparator. Because of the intensity and practice requirements of continuous subcutaneous insulin (CSII) infusion by external pump therapy, and in view of the improved glycemic control that can be achieved with pump therapy versus multiple insulin injections, a randomized comparison of pump therapy and multiple insulin injections would not have been practicable. Near-normal glycemic control is often difficult to achieve in children and adolescents. Given the constraints of the age group, the HbA1c of ~8% in both treatment groups suggests a reasonable treatment success.

7 INTEGRATED REVIEW OF SAFETY

Safety assessments included reports of adverse events and episodes of hypoglycemia, hyperglycemia, and diabetic ketoacidosis; physical examination findings; laboratory test results for hematology, blood chemistry, and insulin antibody binding.

7.1 Methods and Findings

7.1.1 Deaths

No deaths were reported in Study ANA-2181 or Study ANA-1507.

7.1.2 Other Serious Adverse Events

Seven patients reported serious adverse events (SAEs) in Study ANA-2181 and SAEs were reported for four patients in Study ANA-1507. No patients withdrew from the studies as a result of the SAEs. Three patients reported episodes of hypoglycemia (one each) as SAEs in Study ANA-2181 and one patient had an episode of hypoglycemia in Study ANA-1507. One patient reported an episode of diabetic ketoacidosis (after a missed breakfast, disconnection of pump, and injection of a bolus insulin dose). All of the patients recovered from SAEs. The table below summarizes the serious adverse events.

Table 5–2 List of Subjects Reporting SAEs in Trials ANA-2181 and ANA-1507

Subject	Age (Gender)	Treatment	AE (Onset Day)	Outcome	Relationship
Trial ANA-2181					
103	12 (F)	CSII Aspart	Hypoglycaemic seizure (73)	Recovered	Unlikely
1010	13 (F)	CSII Aspart	Diabetic ketoacidosis (30)	Recovered	Unlikely
2006	12 (M)	CSII Aspart	Hypoglycaemia (25) Accidental overdose (of insulin) (25)	Recovered Recovered	Probable Probable
3705	12 (M)	CSII Aspart	Hyperglycaemia (21)	Recovered	Unlikely
5507	15 (M)	CSII Aspart	Skin laceration (23)	Recovered	Unlikely
703	14 (M)	CSII Lispro	Hypoglycaemia (46)	Recovered	Possible
3612[a]	16 (F)	Prior to study drug	Hypoglycaemia (-11), headache (-11), pyrexia (-11)	Recovered	Unlikely
Trial ANA-1507					
27	7 (M)	MIT Aspart	Severe hypoglycaemia (143)	Recovered	Probably
34	5 (F)	MIT Aspart	Acute gastroenterocolitis (166)	Recovered	Unlikely
182[b]	4 (M)	CSII Aspart	Acute tonsillitis (-14)	Recovered	Unlikely
180[b]	5 (M)	CSII Aspart	Gastrointestinal infection (-5)	Recovered	Unlikely

Age is given in years. M = male. F = Female.
a: Subject had an SAE prior to the treatment period but went on to be randomised to CSII insulin lispro and completed the study.
b: Subjects had an SAEs during the run-in period but went on to be allocated to CSII insulin aspart and completed the study.
Cross reference Section 12.3, CTR for ANA-2181 and Section 10.2, CTR for ANA-1507.

7.1.3 Dropouts

One patient treated with insulin lispro withdrew from Study ANA-2181 on Day 13 because of persistent hyperglycemia due to an infusion set problem. No patient withdrew from study ANA-1507.

7.1.3.1 Other significant adverse events

Hypoglycemia

In Study ANA-2181, episodes of hypoglycemia were classified as follows:

- **Major hypoglycemic episode:** An episode with severe central nervous system symptoms consistent with hypoglycemia in which the patient is unable to treat himself/herself, and which had one or both of the following characteristics: Plasma glucose < 56 mg/dL (3.1 mmol/L), or reversal of symptoms after either food intake or glucagon/IV glucose administration.

- **Minor hypoglycemic episode -** An episode with or without symptoms consistent with hypoglycemia with a plasma glucose measurement < 56 mg/dL (< 3.1 mmol/L), which was handled by the patient him/herself;

- **Hypoglycemic symptoms:** Symptoms that were considered to be related to hypoglycaemia but not confirmed by a plasma glucose measurement or a plasma glucose measurement ≥ 56 mg/dL (≥ 3.1 mmol/L) but were rated by the subject/caregiver as symptomatic.

The table below summarizes the episodes of hypoglycemia:

Table 5–4 Analysis of Hypoglycaemic Episodes Reported in Trial ANA-2181

	CSII Aspart (N=198)			CSII Lispro (N=100)			Aspart/Lispro	
Type of Episode	n (%)	E	R	n (%)	E	R	Rate Ratio	95% CI
Total:								
All	190 (96%)	5547	92.2	97 (97%)	2418	81.3	1.13	0.93; 1.38
Major	19 (10%)	25	0.42	8 (8%)	9	0.3	1.37	0.57; 3.32
Minor	188 (95%)	4643	77.2	94 (94%)	1961	66.0	1.17	0.96; 1.43
Symptoms Only	149 (75%)	722	12.0	82 (82%)	394	13.3	0.91	0.62; 1.31
Unclassified	24 (12%)	157	2.6	18 (18%)	54	1.8	1.44	0.39; 5.29
PG ≤36 mg/dL	94 (48%)	301	5.0	41 (41%)	117	3.9	1.27	0.80; 2.02
Nocturnal [a]:								
All	118 (60%)	340	5.7	56 (56%)	184	6.2	0.91	0.62; 1.34
Major	3 (2%)	4	0.1	1 (1%)	1	0.0	1.98	0.17; 23.60
Minor	112 (57%)	293	4.9	47 (47%)	157	5.3	0.92	0.62; 1.38
Symptoms Only	25 (13%)	33	0.6	19 (19%)	23	0.8	0.71	0.38; 1.34
Unclassified	6 (3%)	10	0.2	1 (1%)	3	0.1	1.65	0.18; 15.12
PG ≤36 mg/dL	18 (9%)	25	0.4	8 (8%)	19	0.6	0.65	0.25; 1.69
Daytime:								
All	188 (95%)	5170	85.9	97 (97%)	2206	74.2	1.16	0.95; 1.41
Major	17 (9%)	21	0.4	7 (7%)	8	0.3	1.30	0.52; 3.25
Minor	185 (93%)	4326	71.9	94 (94%)	1780	59.9	1.20	0.98; 1.48
Symptoms Only	148 (75%)	684	11.4	79 (79%)	369	12.4	0.92	0.63; 1.34
Unclassified	24 (12%)	139	2.3	18 (18%)	49	1.7	1.40	0.40; 4.94
PG ≤36 mg/dL	91 (46%)	275	4.6	36 (36%)	96	3.2	1.42	0.88; 2.28

E = number of episodes. R = rate (number of events/subject/year).
a: Events with missing times excluded from Nocturnal (24:00 through 0.5:59).
Cross reference: EOT Table 14.5.5, CTR for ANA-2181.

The percentage of patients with major hypoglycemia was similar for the insulin aspart and insulin lispro treatment groups – for the total, nocturnal, and daytime episodes. Similarly, the frequency of hypoglycemia did not significantly differ between the pump patients and the patients treated with multiple dose insulin regimens in Study ANA-1507.

Table 5–5 Hypoglycaemic Episodes Reported in Trial ANA-1507

Hypoglycaemic	CSII Aspart		MIT Aspart		MIT HI	
Episode	N (%)	E (Rate)	N (%)	E (Rate)	N (%)	E (Rate)
N exposed	20		20		21	
Major Episode	1 (5%)	3 (0.3)	1 (5%)	1 (0.1)	0	0
Minor Episode	17 (85%)	235 (21)	18 (90%)	189 (18)	19 (90%)	242 (20)
Symptoms Only	7 (35%)	14 (1.2)	5 (25%)	12 (1.1)	9 (43%)	17 (1.4)

E=number of episodes. Rate=number of episodes/year of exposure.
Cross Reference: Table 4-4, Module 2.7.4.

Diabetic ketoacidosis (DKA)

Four patients met the criteria for DKA (as outlined in the 2002 ADA Clinical Practice Guidelines) [3 insulin aspart, 1 insulin lispro] in Study ANA-2181. No episodes of DKA were reported in Study ANA-1507.

Hyperglycemia

In Study ANA-2181, hyperglycemia, defined as plasma glucose > 300 mg/dL, was reported by investigators if they considered the hyperglycemia an adverse event. An adverse event of hyperglycemia was reported in 21 (11%) of patients treated with insulin aspart and in 17 (17%) of the patients treated with insulin lispro. Hyperglycemia was not reported as an adverse event in Study ANA-1507.

Infusion Site Reactions

An adverse event of infusion site reaction was reported in 34 (17%) of patients treated with insulin aspart and in 21 (21%) of the patients treated with insulin lispro (p=0.432, Fisher's Exact Test). The most frequently reported infusion site adverse events (i.e., preferred terms) were infusion site erythema and infusion site reaction. The table below summarizes these adverse events.

Table 5–3 Subjects with Infusion Site Reactions in Trial ANA-2181

	CSII Aspart		CSII Lispro	
Preferred Term	**N (%)**	**No. Events**	**N (%)**	**No. Events**
N treated	198		100	
N w/ infusion site reaction	34 (17%)		21 (21%)	
Catheter site related reaction	1 (<1%)	1	3 (3%)	4
Infusion site erythema	11 (6%)	16	6 (6%)	8
Infusion site induration	5 (3%)	7	2 (2%)	2
Infusion site inflammation	1 (<1%)	1	0	0
Infusion site irritation	1 (<1%)	1	3 (3%)	4
Infusion site pruritus	2 (1%)	2	0	0
Infusion site rash	3 (2%)	3	1 (1%)	1
Infusion site reaction	12 (6%)	15	7 (7%)	10
Infusion site swelling	1 (<1%)	1	0	0
Infusion site vesicles	0	0	1 (1%)	1

Cross reference EOT Table 14.5.17 and EOT Table 14.5.6a, CTR for ANA-2181.

7.1.4 Laboratory Findings

No significant differences in mean values for hematology, biochemistry, or urinalysis parameters were observed at the beginning or end of Study ANA-2181. Only baseline screening hematology and chemistry parameters were measured in Study ANA-1507, and these did not differ among the three groups.

7.1.5 Vital Signs

Vital sign assessments were similar for the different treatment groups at all timepoints in both studies.

7.1.6 Immunogenicity

Prior to enrollment in Study ANA-2181, all of the patients were treated with continuous subcutaneous insulin infusion pump therapy. Forty-four percent (44%) were treated with insulin aspart, and 54% were treated with insulin lispro. Not surprisingly, many patients had baseline cross-reacting antibodies.

Table 5. Cross-reacting Antibodies in Study ANA-2181

Treatment Group	Insulin Aspart	Insulin Lispro
Antibodies cross-reacting with regular HI and insulin aspart	% binding, mean (SD) values	% binding, mean (SD) values
• Baseline	30.4 (18.5)	29.6 (20.8)
• Week 16	35.2 (19.6)	28.6 (19.8)
Antibodies cross-reacting with regular HI and insulin lispro		
• Baseline	30.0 (18.3)	29.1 (20.3)
• Week 16	34.6 (19.3)	27.9 (19.3)

The cross-reacting antibodies were not associated with a deterioration in HbA1c or an increased insulin dose requirement.

7.1.7 Assessment of Effect on Growth

The height and weight data for Study ANA-2181 are summarized in the Table below. Whereas weight data were carried forward, the height data are for completers only. For that reason, the population sizes may differ for some of the groups. Based on these data, the effect on growth appeared similar for the aspart and lispro treatment groups. The major reason for this analysis was to confirm that children in both treatment groups were growing during the study. The slight discrepancy in the numbers available for height and weight measurements does not affect the conclusion.

Table 6 . Height and Weight at Baseline and 16 Weeks in Study ANA-2181

Mean (SD, range)	**Aspart**	**Lispro**
N	190	97
Height (cm)		

• **Baseline**	156 (18, 100-196)	158 (17, 109-196)
• **16 weeks**	157 (18, 103-196)	160 (17, 109 – 196)
• **Change**	1.6 (1.6, -1.8 -13.4)	1.7 (1.8, -1.3 – 10.0)
N	196	99
Weight (kg)		
• **Baseline**	54.2 (19.7, 17.2 – 142.5)	55.5 (18.9, 19.8 -121.4)
• **16 weeks**	56.0 (20.1, 17.1 -149.0)	57.1 (19.2, 20.5-124.1)
• **Change**	1.8 (2.1, -4.3 – 8.2)	1.6 (2.1, -2.8-11.0)

Consistent with the height and weight data, a progression in pubertal status (assessed by Tanner staging) was observed in both treatment groups over the 16-week study period.

7.1.8 Postmarketing Experience

Since insulin aspart was granted pediatric exclusivity (5/24/05) and approved for pediatric use (NDA 20-986 S033, approved 9/13/05), the Division of Drug Risk Evaluation summarized the one-year post exclusivity post-marketing spontaneous adverse event reports in the Adverse Event Reporting System (AERS) database. There was a total of 1338 reports for aspart in the AERS database, including 154 (11.5%) pediatric reports. In the year following exclusivity, there was a total of 284 reports for aspart, including 28 (9.9%) pediatric reports. Of the 26 unduplicated pediatric reports, there were 3 deaths, 4 unlabeled events and 19 labeled events. Six events occurred during exposure via maternal use, including four unlabeled events. The post-exclusivity case characteristics summarized in the DDRE safety evaluator's review are cited in the table below. (*Source:* NDA 20-986 1-year Post-Pediatric Exclusivity Post-Marketing Adverse Event Review for NovoLog® (insulin aspart recombinant), J. Swann, 8/24/06, Accessed through the Division File System.)

Table 26. Post-marketing Data – One year post exclusivity

Table 3: Characteristics of Pediatric Cases reported during the pediatric exclusivity approval through AERS cut-off date (May 24, 2005 through June 24, 2006) N=26	
Gender	n=25
Female	11
Male	14
Age at time of event	
0 < 1 month	6
1 month < 2 yrs	2
2-5 yrs	3
6-11 yrs	6
12-16 yrs	9
Mean	7.3 yrs
Median	8.0 yrs
Range	4 days-15 yrs
Origin	
US	17
Foreign	9
Event date	n=25
2003	2
2004	6
2005	16
2006	1
Time to Event, (days)	n=11
Mean	264
Median	122
Range	1-1214
Indications	
Type 1 diabetes mellitus	20
Exposure via Maternal Use	6
Outcomes†	
Congenital Anomaly	3
Death	3
Disability	1
Hospitalization	14
Life-Threatening	5
Other	9
Required intervention	5

† Outcomes are not mutually exclusive; one case could contain more than one outcome.

Two fatal congenital malformations were described in infants exposed to maternal insulin aspart: a case of *truncus arteriosus communis*, and a case of hypoxic ischemic encephalopathy and fetal distress at birth. Non-fatal *in utero* exposure events were described in the following four cases: (1) neonatal hypoglycemia and a congenital anomaly (ankyloglossia); (2) urinary retention, neonatal asphyxia, and a hypoxic-ischemic lesion of the central nervous system; (3) dysmorphy of the right frontal lobe, increased frontal subarachnoid space, and asymmetry of the lateral ventricle; and (4) neonatal hypoglycemia. In a spontaneous reporting system such as AERS, it is not possible to distinguish whether the *in utero* exposure events, including congenital malformations and neonatal hypoglycemia, were secondary to insulin aspart or to the underlying maternal diabetic milieu, as these events occur relatively frequently (>5%) in controlled clinical trials. AERS data are better suited for signal detection of rare, serious, or life-threatening events. No recommendations for label changes were made on the basis of this post-marketing analysis.

For the conversion of the prescribing information to the PLR format, a consult regarding cases of anaphylaxis was requested from the Office of Surveillance and Epidemiology (J. Swann, January 17, 2008)7.
The following case definition for anaphylaxis was cited:

Case definition for anaphylaxis4:
1. Clinical diagnosis of anaphylaxis (reports submitted by a healthcare professional) OR
2. If skin or mucosal tissue involvement (e.g., urticaria, angioedema, pruritus, and flushing)
AND one of the following:
a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, hypoxemia),
or
b) Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g.,
hypotension, syncope, hypotonia [collapse]).

In a review of the FDA spontaneous Adverse Event Reporting System (AERS), 23 cases with hypersensitivity or anaphylaxis were identified with aspart (NovoLog®) treatment. Of these, thirteen were thought to meet the case definition for anaphylaxis by the safety evaluator. In reviewing these cases, the clinical reviewer noted that three of these thirteen cases did not discontinue treatment with aspart. The absence of discontinuation of aspart makes a clinical diagnosis of anaphylaxis less plausible. However, there were at least 3 cases (ID numbers 39, 40, 46 in J. Swan's review) that met the case definition for anaphylaxis, discontinued treatment with aspart, and were not treated with other confounding concurrent medications. On this basis, the inclusion of the term 'anaphylaxis' in the prescribing information appears justified, based on the post-marketing case reports.

8 OVERALL ASSESSMENT

8.1 Conclusions

The purpose of external insulin pump therapy is maximal improvement of glycemic control and not just a convenience factor. The data from the studies submitted by Novo Nordisk (Study ANA-2181 and Study ANA-1507) support the safety and effectiveness of insulin aspart continuous subcutaneous insulin infusion by external pump in the pediatric population. Insulin aspart and insulin lispro treatments by external pump resulted in similar efficacy, and the findings were similar to those observed in studies in adults.

8.2 Recommendation on Regulatory Action

This clinical reviewer recommends approval of this efficacy supplement. Specifically, this reviewer recommends approval of the following:

7 NDA 20-986 047 Review of Serious Hypersensitivity Events, J. Swann, Pharm.D., January 17, 2008

- the pediatric indication of continuous subcutaneous insulin infusion (CSII) by external insulin pump for treatment of hyperglycemia in patients with type 1 diabetes mellitus;
- the prescribing information for NovoLog insulin analog (Insulin Aspart (Asp) [rDNA origin]) in the revised Physician Labeling Rule (PLR) format8, pending agreement with FDA modifications. a waiver for children ages three and younger, as there are inadequate number of children in this age group for study, and efficacy and safety data are not expected to differ from those observed in older children.

Additional Recommendation Regarding Pediatric Intravenous Administration of NovoLog®

The intravenous indication for NovoLog was based on an adult pharmacokinetic pharmacodynamic study and it was approved on October 21, 2005. The pediatric intravenous indication was not specifically mentioned in the approval letter for the intravenous indication. In fact, that letter stated the following:

"All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application."

Presumably the last sentence referred to the original pediatric subcutaneous indication for aspart, which was approved on September 13, 2004

Recommendation:

This reviewer recommends that we waive the requirement for the pediatric intravenous study. There is no physiologic reason to suspect intravenous insulin would act differently in the pediatric population. Intravenous insulin should be administered in a hospital setting by trained personnel, so the 'in use' aspect that is evaluated in clinical studies should also not differ. This topic was discussed with members of the FDA Pediatric Review Committee. They concurred that the product is already appropriately labeled in the pediatric population and further pediatric studies for the pediatric indication are not needed. The Pediatric Review Committee has proposed the following language:

All applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. This drug product (NovoLog®) is fully labeled for use in all appropriate pediatric populations. Therefore, no additional pediatric studies are needed at this time.

8 21CFR201.57, Revised as of April 1, 2006.

8.3 Recommendation on Postmarketing Actions

8.3.1 Risk Management Activity

Other than the modifications in the prescribing information, no other specific risk management activities are recommended.

8.3.2 Required Phase 4 Commitments

No new Phase 4 commitments are requested.

8.3.3 Other Phase 4 Requests

There are no other Phase 4 requests.

8.4 Labeling Review

A red-lined version of the label, with comments from CMC, clinical pharmacology, and statistics is attached to this review. Pharmacology/toxicology had no changes.

Because the submission of an efficacy supplement triggered conversion of labeling to the PLR format, Novo Nordisk was advised to submit a label with changes similar to the ones this reviewer and others in the team had made in the PLR version of the [redacted (b) (4)]

This clinical reviewer has made additional changes to the label based on the following:

- a word-by-word comparison of the PLR label to the previously approved (4/07 non-PLR) version.
- changes we made to format the NovoLog Mix [redacted (b) (4)] label from the non-PLR format [redacted (b) (4)]) 9
- review of current European Medicines Agency (EMEA) aspart (NovoRapid®) label 10

[redacted (b) (4)]

10 EMEA label for aspart (NovoRapid®) accessed electronically at http://www.emea.europa.eu/humandocs/PDFs/EPAR/Novorapid/H-258-PI-en.pdf

- review of other US-approved insulin labels 11 (including the NovoLog [redacted] (b) (4)

- review of prior FDA medical officer and clinical pharmacology reviews of NovoLog submissions for subcutaneous, pump, and intravenous use 12

- review of prior FDA medical officer and clinical pharmacology reviews of lispro (Humalog®, Lilly) submissions for subcutaneous and pump use 13

- review of Office of Surveillance and Epidemiology consult and the cited 23 postmarketing cases of hypersensitivity and/or anaphylaxis14

Per FDA instructions (including specific table schemata), Novo Nordisk completed a number of tables, including the following:

- tables of emergent adverse events during Type 1 and Type 2 clinical trials *(Section 6);*

- tables summarizing the key efficacy and safety parameters for the various referenced clinical trials *(Section 14).*

The schemata for these tables are included. I have suggested the same table format for the various clinical trials cited, for easier readability. There are a number of additional questions for the company in the comments.

The current indication (with FDA changes) states :

> NovoLog® is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus (1.1)

The DOSAGE AND ADMINISTRATION section outlines the three modes of administration (cited from the Highlights page):

- The dosage of NovoLog® must be individualized.

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11 insulin labels accessed electronically at Drugs@FDA

12 NDA 20-986 Clinical Review of aspart, E. Koller, M.D., August 1999.
NDA 20-986 003 Clinical Review of aspart for external pump use in adults, E. Koller, M.D, December 21, 2001
NDA 20-986 003 Division Director Review of aspart for external pump use in adults, D. Orloff, M.D, December 21, 2001
NDA 20-986 033 Clinical Review of pediatric subcutaneous aspart use, E. Koller, M.D., September 2005
NDA 20-986 032 Clinical Review of intravenous aspart use, E. Gabry, M.D., October 11, 2005
NDA 20-986 040 Action Letter approval of diluent, October 27, 2006
13 NDA 20-563 Clinical Review of lispro, E. Koller, M.D., June 2004.
NDA 20-986 003 Clinical Review of aspart for external pump use in adults, E. Koller, M.D, December 21, 2001
NDA 20-986 003 Division Director Review of aspart for external pump use in adults, D. Orloff, M.D, December 21, 2001
NDA 20-986 033 Clinical Review of pediatric subcutaneous aspart use, E. Koller, M.D., September 2005
NDA 20-986 032 Clinical Review of intravenous aspart use, E. Gabry, M.D., October 11, 2005
NDA 20-986 040 Action Letter approval of diluent, October 27, 2006
14 NDA 20-986 047 Review of Serious Hypersensitivity Events, J. Swann, Pharm.D., January 17, 2008

- *Subcutaneous injection:* NovoLog® should generally be given immediately (within 5-10 minuties) prior to the start of a meal (2.1)
- *Use in pumps*: Change the NovoLog® in the reservoir, the infusion set, and the infusion set insertion site at least every 48 hours. NovoLog® should not be mixed with other insulins or with a diluent when it is used in the pump. (2. 3)
- *Intravenous use*: NovoLog® should be used at concentrations from 0.05 U/mL to 1.0 U/mL insulin aspart in infusion systems using polypropylene infusion bags. NovoLog has been shown to be stable in infusion fluids such as 0.9% sodium chloride. (2.3)

Of note, the Study Endpoints and label Development (SEALD) team had been consulted to review the PLR label for insulin aspart, after the Division had completed its revisions. On February 25, 2008, the SEALD team announced that it no longer reviews PLR labels for already approved drugs.

The patient label and the product information for vials, cartridges and pens were modified to match the physician PLR prescribing information after agreement between FDA and Novo Nordisk was reached.

Intravenous aspart use

The Dosage and Administration section of the Highlights page of the PLR reads as follows:

·DOSAGE AND ADMINISTRATION·····
- The dosage of NovoLog® must be individualized.
- *Subcutaneous injection:* NovoLog® should generally be given immediately (within 5-10 minuties) prior to the start of a meal (2.1)
- *Use in pumps*: Change the NovoLog® in the reservoir, the infusion set, and the infusion set insertion site at least every 48 hours. NovoLog® should not be mixed with other insulins or with a diluent when it is used in the pump. (2.3)
- *Intravenous use*: NovoLog® should be used at concentrations from 0.05 U/mL to 1.0 U/mL insulin aspart in infusion systems using polypropylene infusion bags. NovoLog has been shown to be stable in infusion fluids such as 0.9% sodium chloride, 5% dextrose, or 10% dextrose with 40 mmol/l potassium chloride using polypropylene infusion bags. (2.3)

Use of intravenous insulin aspart was previously approved with the wording cited above. The data for the three infusion fluids (0.9% sodium chloride, 5% dextrose, or 10% dextrose) was presented in an amendment to the intravenous insulin supplement.15 Note that potassium was added only to the 10% dextrose solution but not to the other solutions. The data are summarized in the table below:

15 Hennigan, BB. *White Paper: Intravenous Use of Insulin Aspart and Regular Human Insulin in the Acute Management of Hyperglycemia and its Complications in Patients in a Hospital Setting.* Submitted as amendment to NDA 20-986 032, August 1, 2005.

Table 2 Minimum and Average Recovery of Insulin (%) from Infusion Fluids

Insulin (U/mL)	Infusion Fluid	-------- Insulin aspart-------- Minimum Recovery (%)	Average Recovery (%)	-------- Human Insulin -------- Minimum Recovery (%)	Average Recovery (%)
0.05	0.9% NaCl	84.9	87.2	75.9	80.8
0.2	0.9% NaCl	91.2	94.2	89.8	94.2
1.0	0.9% NaCl	96.4	97.4	98.5	99.2
0.05	5% Glucose	81.3	83.9	70.3	76.2
0.2	5% Glucose	89.7	91.6	86.2	87.5
1.0	5% Glucose	97.7	98.6	88.4	92.6
0.05	10% Glucose, 40 mM KCl	85.7	88.2	68.0	76.4
0.2	10% Glucose, 40 mM KCl	91.1	93.1	87.6	91.1
1.0	10% Glucose, 40 mM KCl	96.8	97.8	94.2	96.8

Additional Recommendation Regarding Pediatric Intravenous Administration of NovoLog®

The intravenous indication for NovoLog was based on an adult pharmacokinetic pharmacodynamic study and it was approved on October 21, 2005. The pediatric intravenous indication was not specifically mentioned in the approval letter for the intravenous indication. In fact, that letter stated the following:

"All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application."

Presumably the last sentence referred to the original pediatric subcutaneous indication for aspart, which was approved on September 13, 2004

Recommendation:
This reviewer recommends that we waive the requirement for the pediatric intravenous study. There is no physiologic reason to suspect intravenous insulin would act differently in the pediatric population. Intravenous insulin should be administered in a hospital setting by trained personnel, so the 'in use' aspect that is evaluated in clinical studies should also not differ. This topic was discussed with members of the FDA Pediatric Review Committee. They concurred that the product is already appropriately labeled in the pediatric population and further pediatric studies for the pediatric indication are not needed. The Pediatric Review Committee has proposed the following language:

All applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. This drug product (NovoLog®) is fully labeled for use in all appropriate pediatric populations. Therefore, no additional pediatric studies are needed at this time.

Comments to Applicant

Comments have been conveyed to the applicant electronically in the multiple line-by-line red-lined labeling reviews discussed above.

9 APPENDICES

9.1 Line-by-Line Labeling Review

Please see attached label, which incorporates the changes described in the labeling review and the multiple negotiations described below. The following are attached to this review, but they are entered into the Division File System separately because of the tracked changes.

- Physician Labeling for NovoLog® in the Physician Labeling Rule format
- Patient Labeling for NovoLog®

There are three sets of Instructions for Use. These instructions were not significantly modified by the clinical reviewer and they are not included in this review *per se*.

- Instructions for Use for Vial
- Instructions for Use for cartridge
- Instructions for Use for pen

The label was revised by FDA and forwarded to Novo Nordisk on February 11, 2008. Novo Nordisk submitted a revised label on February 15, 2008, and additional FDA revisions were forwarded to Novo Nordisk on February 20, 2008. The patient label and Instructions for Use were reviewed by the Division of Risk, Office of Surveillance and Epidemiology. Additional changes in the physician label, patient label, and three sets of Instructions for Use (vial, cartridge, pen) were made and forwarded to the sponsor on March 7, 2008. Novo Nordisk responded with additional minor changes on March 11, 2008, which were discussed in a teleconference with Novo Nordisk on March 12, 2008. The attached label is the label that was finalized as of March 12, 2008. (Please note – others at FDA may recommend additional modifications; this labeling has not yet been deemed the final labeling for this supplement.)

REFERENCES

1. NovoLog® (insulin aspart) package insert, Novo Nordisk. January 26, 2007.
2. Hyperglycaemic crises in patients with diabetes mellitus: Position statement from the American Diabetes Association. *Diabetes Care*. 2002;25(Suppl 1):S100-S108.
3. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J of Med.* 1993;329(14):977-986
4. Phillip M, Battelino T, Rodriguez H, Danne T, Kaufman F. Consensus statement on the use of insulin pump therapy in the pediatric age group. *Diabetes Care.* Available online March 19, 2007.
5. Tamborlane WV, Sikes KA, Steffen AT, Weinzimer SA. Continuous subcutaneous insulin infusion (CSII) in children with type 1 diabetes. *Diabetes Research and Clinical Practice.* 2006;74:S112-S115.

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/s/

Joanna Zawadzki
3/12/2008 07:08:10 PM
MEDICAL OFFICER

Hylton Joffe
3/12/2008 08:29:49 PM
MEDICAL OFFICER
Please see clinical team leader memo.

Mary Parks
3/13/2008 09:39:26 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020986/S-047

CHEMISTRY REVIEW(S)

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER
	DMEDP II, HFD-510	20-986
3. NAME AND ADDRESS OF APPLICANT		**4. COMMUNICATION, DATE**
Novo Nordisk Pharmaceuticals, Inc. Suite 200, 100 Overlook Center Princeton NJ 08450		SE5-047, 11-May-2007
5. PROPRIETARY NAME	**6. NAME OF THE DRUG**	**7. AMENDMENTS, REPORT, DATE**
Novolog®	Insulin aspart (rDNA origin) injection	SE5-047BL, 16-Jan-2008 SE5-047BL, 12-Nov-2007

8. COMMUNICATION PROVIDES FOR:

Clinical data to fulfill a pediatric postmarketing study commitment under section 2 of the Pediatric Research Equity Act.

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Antihyperglycemic	RX	
12. DOSAGE FORM	**13. POTENCY**	
Solution for injection	100 U/mL	
14. CHEMICAL NAME AND STRUCTURE		

See Chemistry Review #1

15. COMMENTS

This efficacy supplement includes clinical data to support external continuous subcutaneous infusion of insulin aspart for pediatric use. CMC information provided in this supplement (b) (4)

Continued on the next page.

16. CONCLUSION AND RECOMMENDATION

The applicant (b) (4) The CMC labeling comments that should be forwarded to the applicant. Once the CMC labeling changes have been made, from a CMC standpoint this supplement can be approved.

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
JANICE BROWN	See appended electronic signature sheet	30-Jan-2008

DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE

Chemist's Review Notes

1. [redacted].

2. CMC Comments: PLR – PI - Full Prescribing Information

   i. Section 2.1 Dosing

   Delete: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

   ii. Section 3 DOSAGE FORMS AND STRENGTHS

   The applicant has added the following dosage forms: 3mL PenFill® cartridge compatible insulin delivery devices, [redacted].

   Evaluation: The potency of insulin aspart was provided and a description of the dosage form was provided. The proposed changes are acceptable.

   iii. Section 11 DESCRIPTION

   There are no changes to the description.

   Evaluation: Acceptable.

   iii. Section 16.2 Recommended Storage

   1. Add a title and header to separate the table from the other presentations. For example:

   Summary of Storage Conditions:

   Table X: Storage conditions for vial, PenFill cartridges and NovoLog FlexPen Prefilled syringe

Novolog presentation	Not in-use (unopened) Room Temperature (below 30°C)	Not in-use (unopened) Refrigerated	In-use (opened) Room Temperature (below 30°C)
10 mL vial	28 days	Until expiration date	28 days (refrigerated/room

			temperature)
3 mL PenFill cartridges	28 days	Until expiration date	28 days (Do not refrigerate)
3 mL NovoLog FlexPen Prefilled syringe	28 days	Until expiration date	28 days (Do not refrigerate)

2. Add a header to separate the storage conditions of diluted insulin (e.g., ***Storage of Diluted Novolog).***

Revise: NovoLog® [redacted (b) (4)]

To: NovoLog [redacted (b) (4)].

3. Add a header to separate the storage conditions of infusion bags (e.g., ***Storage of Novolog in Infusion Fluids).***

Revise: Infusion bags prepared as indicated under *Dosage and Administration (2)* are stable at room temperature for 24 hours. [redacted (b) (4)]

To: Infusion bags prepared as indicated under *Dosage and Administration,* [redacted (b) (4)]

3. CMC Comments: Patient Information for NovoLog Vial

a. Under "How should I store Novolog?"

i. Second bullet: [redacted (b) (4)]

ii. Third bullet

Revise: NovoLog® in the pump reservoir and the complete [redacted (b) (4)].

To: NovoLog in the pump reservoir and the complete [redacted (b) (4)]

4. CMC Comments: Patient Information for NovoLog Flexpen Prefilled Syringe

5. CMC Comments: Patient Information for NovoLog PenFill

    a. See comment in item 3(a)(ii).

6. After the CMC labeling changes have been made, from a CMC standpoint this supplement can be approved.

LABELING COMMENTS THAT SHOULD BE FORWARDED TO THE APPLICANT

1. CMC Comments: PLR – PI - Full Prescribing Information

   a. Section 2.1 Dosing

      Delete: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

   b. Section 16.2 Recommended Storage

      i. Add a title and header to separate the table from the other presentations. For example:

      Summary of Storage Conditions:

      Table X: Storage conditions for vial, PenFill cartridges and NovoLog FlexPen Prefilled syringe

Novolog presentation	Not in-use (unopened) Room Temperature (below 30°C)	Not in-use (unopened) Refrigerated	In-use (opened) Room Temperature (below 30°C)
10 mL vial	28 days	Until expiration date	28 days (refrigerated/room temperature)
3 mL PenFill cartridges	28 days	Until expiration date	28 days (Do not refrigerate)
3 mL NovoLog FlexPen Prefilled syringe	28 days	Until expiration date	28 days (Do not refrigerate)

      ii. Add a header to separate storage conditions of diluted insulin (e.g., ***Storage of Diluted Novolog).***

      Revise: NovoLog® (b) (4)

      To: NovoLog® (b) (4)

      iii. Add a header to separate storage conditions of infusion bags (e.g., ***Storage of Novolog in Infusion Fluids).***

      Revise: Infusion bags prepared as indicated under *Dosage and Administration (2)* are stable at room temperature for 24 hours. (b) (4) .

To: Infusion bags prepared as indicated under *Dosage and Administration,* (b) (4)

2. CMC Comments: Patient Information for NovoLog Vial

   a. Under "How should I store Novolog?"

      i. Second bullet: (b) (4)

      ii. Third bullet

      Revise: NovoLog® in the pump reservoir (b) (4)

      To: NovoLog® in the pump reservoir (b) (4)

3. CMC Comments: Patient Information for NovoLog Flexpen Prefilled Syringe

(b) (4)

4. CMC Comments: Patient Information for NovoLog PenFill

   a. See comment in item 3(a)(ii).

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Janice Brown
1/31/2008 12:53:14 PM
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Jim Vidra
2/1/2008 04:18:16 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020986/S-047

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	20-986/SE5-047
Drug Name:	NovoLog (insulin aspart [rDNA origin] injection)
Indication(s):	• Treatment of patients (children and adults) with diabetes mellitus • Subcutaneous infusion by external insulin pumps (children and adults) • Intravenous administration
Applicant:	Novo Nordisk
Date(s):	Received 5/11/07; user fee (10 months) 3/14/08
Review Priority:	Standard
Biometrics Division:	DB 2
Statistical Reviewer:	Lee-Ping Pian, Ph.D.
Concurring Reviewers:	Todd Sahlroot, Ph.D.
Medical Division:	Division of Metabolism and Endocrinology Products (DMEP)
Clinical Team:	Joanna K. Zawadzki, M.D.
Project Manager:	Rachel Hartford

Keywords: NDA review, clinical studies

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This supplemental application provided the required clinical data to fulfill a pediatric postmarketing study commitment for the external insulin pump use (supplement S-003, letter dated December 21, 2001).

Study ANA-2181 was an open-label, randomized, parallel group, multicenter study of 16 weeks to assess external continuous subcutaneous infusion (CSII) of Insulin Aspart (NovoLog) versus Insulin Lispro (Humalog) in children and adolescents 3 to 18 years of age with Type 1 Diabetes who had $HbA_{1c} \leq 10\%$ at baseline.

The primary efficacy comparison was non-inferiority of aspart to insulin lispro in HbA_{1c} change from baseline to Week 16 using a margin of 0.4%.

A total of 298 patients were randomized; 198 to Aspart and 100 to Lispro. 187 patients in the Aspart group and 91 in the Lispro group completed the study. The per protocol population included 252 (85%) of the randomized patients (172 Aspart and 80 Lispro). Table 1 displays the descriptive statistics of HbA_{1c}. Table 2 displays the analysis of covariance (ANCOVA) results in the least squares mean (LSM) in HbA_{1c} changes from baseline to week 16 for the full analysis set (FAS) using last observation carried forward (LOCF) to impute missing data. The upper confidence interval, 0.07% is less than the 0.4% non-inferiority margin which indicated the pump treatment of Aspart is non inferior to Lispro in HbA_{1c} change from baseline (Table 2). ANCOVA results from the per protocol (PP) population were similar. Figure 1 displays the HbA_{1c} values by visit using PP population. completers (187 Aspart and 91 Lispro).

Table 1 Mean change (SD) from baseline in HbA_{1c} (%) at Week 16 – FAS, LOCF

Treatment	N	Baseline	Week 16	Change
IAsp	192	8.02 (0.94)	7.88 (0.93)	-0.13 (0.79)
Lispro	96	8.14 (0.85)	8.07 (0.85)	-0.08 (0.70)

Table 2 Least squares mean change from baseline in HbA_{1c} (%) at Week 16 – ANCOVA* (LOCF)

Treatment	n	LSMean	StdErr	Lower CL	Upper CL
INSULIN ASPART	192	-0.24	0.08	-0.40	-0.07
INSULIN LISPRO	96	-0.13	0.10	-0.33	0.06
ASPART minus LISPRO		**-0.10**	**(0.09)**	**[-0.27**	**0.07]**

*ANCOVA model included treatment group and age group as fixed effects and Baseline HbA_{1c} as covariate

Figure 1 Mean HbA_{1c} (%) by visit - Completers

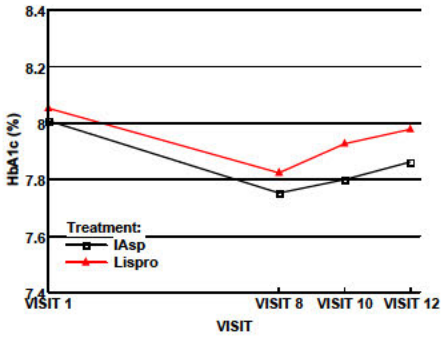
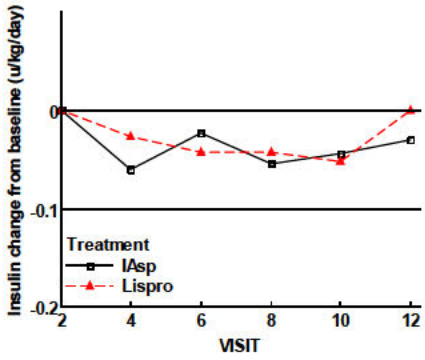


Figure 2 Mean insulin change from baseline by visit - Completers



1.2 Data Sources

Datasets are located at \\CDSESUB1\N20986\S_047\2007-05-11\m5\datasets\2181

2. LABELING COMMENTS

1. Table 1 in the proposed labeling needs to display the number of patients for the ITT population, HbA_{1c} change from baseline and the LSM difference and the 95% confidence interval for the mean difference between NovoLog and Insulin Lispro.

2. The results for [redacted] (b) (4)

3. Results for (b) (4) [redacted]

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/s/

Lee-Ping Pian
3/25/2008 05:18:29 PM
BIOMETRICS

Todd Sahlroot
3/26/2008 03:39:01 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020986/S-047

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

Memo to File

NDA:	20-986 (S047)
Drug:	Novolog (Insulin aspart [rDNA origin] injection) solution for subcutaneous use
Sponsor:	Novo Nordisk
Submission Date:	5/11/2007
Indication:	To improve glycemic control in adults and children with diabetes mellitus
Reviewer:	Jayabharathi Vaidyanathan, Ph.D
Team Leader:	Sally Choe, Ph.D

Recommendations: The information in NDA 20-986/S047 (Novolog) was reviewed by the Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 (OCP/DCP-2). The following labeling comments were sent to the sponsor.

~~(Strikeout text~~ should be removed from labeling and underlined text should be added to labeling.)

7 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, pramlintide, 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), atypical antipsychotics.
- 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.
- The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic products such as beta-blockers, clonidine, guanethidine, and reserpine (b) (4)

12 CLINICAL PHARMACOLOGY

(b) (4)

Pharmacodynamics

Studies in normal volunteers and patients with diabetes demonstrated that subcutaneous administration of NovoLog® has a more rapid onset of action than regular human insulin.

In a study in patients with type 1 diabetes (n=22), the maximum glucose-lowering effect of NovoLog® occurred between 1 and 3 hours after subcutaneous injection (see Figure 2). The duration of action for NovoLog® is 3 to 5 hours (b) (4) . The time course of action of insulin and insulin analogs such as NovoLog may vary considerably in different individuals or within the same individual. The parameters of NovoLog® activity (time of onset, peak time and duration) as designated in Figure 2 should be considered only as general guidelines. The rate of insulin absorption and onset of activity is affected by the site of injection, exercise, and other variables [*see Warnings and Precautions (5.1)*].

Specific Populations

Obesity - (b) (4) -

Renal Impairment - Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. A single subcutaneous dose of (b) (4) Careful glucose monitoring and dose adjustments of insulin, including NovoLog , may be necessary in patients with renal dysfunction [*see Warnings and Precautions* (b) (4)

Hepatic Impairment - Some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. (b) (4) was found between the degree of hepatic failure and any NovoLog pharmacokinetic parameter. Careful glucose monitoring and dose adjustments of insulin, including NovoLog®, may be necessary in patients with hepatic dysfunction [*see Warnings and Precautions* (b) (4) .

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/s/

Jayabharathi Vaidyanathan
3/17/2008 02:01:48 PM
BIOPHARMACEUTICS

Sally Choe
3/25/2008 10:44:17 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020986/S-047

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	March 4, 2008
To:	Mary Parks, M.D., Director Division of Metabolism and Endocrinology Products
Through:	Jodi Duckhorn, M.A., Team Leader Patient Labeling and Education Team Division of Risk Management
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist Patient Labeling and Education Team Division of Risk Management
Subject:	DRISK Review of Patient Labeling (Patient Package Insert and Patient Instructions for Use)
Drug Name(s):	NovoLog (insulin aspart [rDNA origin] injection)
Application Type/Number:	NDA 20-986
Submission Number:	S-047
Applicant/sponsor:	Novo Nordisk
OSE RCM #:	2007-2372

1 INTRODUCTION

Novo Nordisk received approval of their original New Drug Application (NDA) #22-986 on June 7, 2000. This new drug application provides for the use of NovoLog, NovoLog PenFill, and NovoLog Prefilled for the treatment of [redacted] (b) (4)

Novo Nordisk received approval of a Supplemental NDA, sNDA22-986/S-033 on September 13, 2005 altering the patient population. This supplemental new drug application provides for revision to the Pediatric Use subsection of the PRECAUTIONS section of the Package Insert for the use of NovoLog in patients 6 through 18 years old. The Indications and Usage section of the Package Insert was modified as follows: **"**NovoLog is indicated for the treatment of patients with diabetes mellitus, for the control of hyperglycemia."

The sponsor submitted a Supplemental NDA, sNDA 20-986/S-047 on May 11, 2007. The sponsor states in their cover letter that the PREA commitment study "ANA-2181: External Continuous Subcutaneous Infusion of Insulin Aspart (NovoLog) versus Insulin Lispro (Humalog): An Open-Label, Randomized, Parallel Group, Multicentre Study in Children and Adolescents with Type 1 Diabetes" supports theNovoLog label update to include clinical data on pediatric pump use.

DRISK was requested to review three Patient Package Inserts (PPI) attached to separate Patient Instructions of Use, submitted on 8/29/07 for this supplement. Based on comments in relation to the PPI and Patient Instructions for Use for NovoLog 50/50, the review division requested that the sponsor submit on PPI and 3 separate Patient Instructions for Use, one for each product formulation. The sponsor later submitted a revised common PPI attached to 3 individual Patient Instructions for use for NovoLog vial, 3 mL PenFill® cartridge, and for FlexPen® prefilled syringe on January 16, 2008

2 MATERIAL REVIEWED

- 3 NovoLog Revised Proposed Patient Instructions for Use submitted on January 16, 2008, with one common PPI attached to each.
- NovoLog Prescribing Information (PI) submitted, further revised by the review division and sponsor. Resubmitted by the sponsor on February 28, 2008.

3 DISCUSSION

The purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

In our review of the PPI, we have:

- separated the PPI from the Patient Instructions for Use
- simplified wording where possible,

- made it consistent with the Professional Information,
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the PPI. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised PPI. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the PPI.

4 CONCLUSIONS AND RECOMMENDATIONS

1. We request that the review division provide further clarification to the sponsor for future submissions. For review purposes, there should be one separate PPI for the product submitted along with individual Patient Instructions for Use for each individual product formulation. When the NDA or supplemental NDA is approved, the sponsor may for distribution purposes attach the appropriate Patient Instructions for Use to the one PPI and package it with the appropriate product formulation.
2. The verbatim statement "Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088" is required for Medication Guides. (b) (4) [redacted], we recommend including this information in the PPI section "What are the possible side effects of NovoLog?"
3. The three Patient Instructions for Use should have labeled diagrams to illustrate the steps for using the three formulations. The sponsor should update these appropriately and reference the diagrams in the text.
4. The 3 mL PreFilled cartridge Patient Instructions for Use includes (b) (4) [redacted] based on discussion with the review division Medical Officer. Our understanding is that (b) (4) [redacted]

Please let us know if you have any questions.

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/s/

Sharon Mills
3/4/2008 06:59:38 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
3/4/2008 07:59:01 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020986/S-047

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-986/S-047 PRIOR APPROVAL SUPPLEMENT

Novo Nordisk, Inc.
Attn: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. McElligott:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	NovoLog® (insulin aspart [rDNA origin] injection)
NDA Number:	20-986
Supplement number:	047
Review Priority Classification:	Standard (S)
Date of supplement:	May 11, 2007
Date of receipt:	May 14, 2007

This supplemental application provides the required clinical data to fulfill your pediatric postmarketing study commitment under section 2 of the Pediatric Research Equity Act.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 13, 2007, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 14, 2008.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted pediatric studies with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism & Endocrinology Products
Attention: Document and Records Section
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at 301-796-0331 or me at 301-796-1211.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Enid Galliers

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