CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020986Orig1s040

Trade Name: NOVOLOG®

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

Sponsor: Novo Nordisk Inc.

Approval Date: 10/27/2006

Indication: NovoLog is indicated for the treatment of patients with diabetes mellitus, for the control of hyperglycemia. Because NovoLog has a more rapid onset and a shorter duration of activity than human regular insulin, NovoLog given by injection should normally be used in regimens with an intermediate or long-acting insulin. NovoLog may also be infused subcutaneously by external insulin pumps. NovoLog may be administered intravenously under proper medical supervision in a clinical setting for glycemic control.

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APPLICATION NUMBER:

NDA 020986/S-040

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APPLICATION NUMBER:

NDA 020986/S-040

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-986/S-040

Novo Nordisk Inc.
Attention: Mary Ann McElligott, PhD
AVP, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. McElligott:

Please refer to your supplemental new drug application dated June 29, 2006, received June 29, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NovoLog (insulin aspart [rDNA origin]) Injection, 100 Units/mL.

This supplemental new drug application provides for an insulin diluting medium to be used with NovoLog, "Insulin Diluting Medium for NovoLog."

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

The final printed labeling (FPL) must be identical to the enclosed labeling (package insert submitted June 29, 2006, immediate container and carton labels submitted June 29, 2006).

Submit 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 in content to the enclosed labeling text (submitted June 29, 2006. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

Please submit an electronic version of the FPL or you may submit 20 paper copies of the FPL as soon as it is available (no more than 30 days after it is printed). If you submit paper FPL, individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 20-986/S-040.**" Approval of this submission by FDA is not required before the labeling is used.

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

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

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 Enid Galliers, Supervisory Project Manager, at (301) 796-1211.

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
Container Label
Carton Label

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

10/27/2006 05:24:39 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020986/S-040

LABELING

NovoLog®
Insulin aspart (rDNA origin) Injection

DESCRIPTION

NovoLog® (insulin aspart [rDNA origin] injection) is a human insulin analog that is a rapid-acting, parenteral blood glucose-lowering agent. 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) as the production organism. Insulin aspart has the empirical formula $C_{256}H_{381}N_{65}0_{79}S_6$ and a molecular weight of 5825.8.

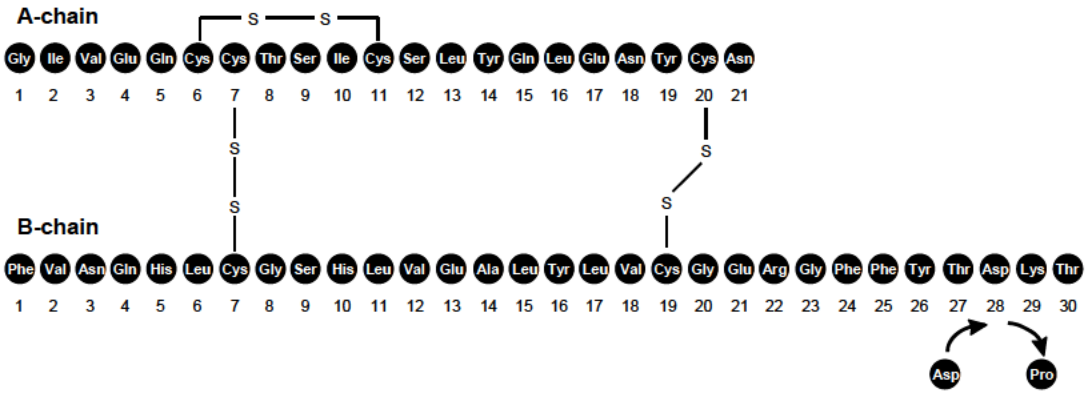


Figure 1. Structural formula of insulin aspart.

NovoLog is a sterile, aqueous, clear, and colorless solution, that contains insulin aspart (B28 asp regular human insulin analog) 100 Units/mL, glycerin 16 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 19.6 µg/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.

CLINICAL PHARMACOLOGY

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.

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 Figure 2 and Figure 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 1.22 l/h/kg for the NovoLog group and 1.24 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 3). The relative bioavailability of NovoLog compared to regular human insulin indicates that the two insulins are absorbed to a similar extent.

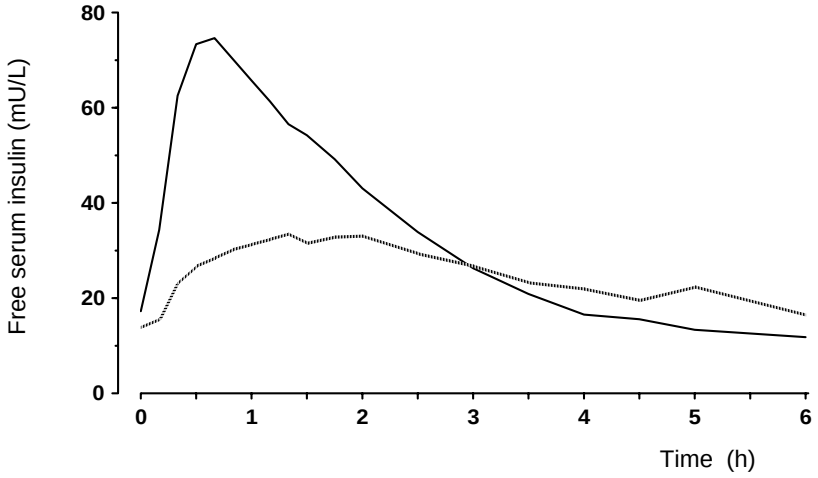


Figure 2. Serial mean serum free insulin concentration collected up to 6 hours following a single pre-meal dose of NovoLog (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with Type 1 diabetes.

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 82.1 and 35.9 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 injection site (abdomen, thigh, or upper arm). Differences in pharmacokinetics between NovoLog and regular human insulin are not associated with differences in overall glycemic control.

Distribution and Elimination - NovoLog has a low binding to plasma proteins, 0-9%, similar to 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.

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 6-hour 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 3). The duration of action for NovoLog is 3 to 5 hours compared to 5 to 8 hours for regular human insulin. 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 3 should be considered only as general guidelines. The rate of insulin absorption and consequently the onset of activity is known to be affected by the site of injection, exercise, and other variables (see PRECAUTIONS, General). Differences in pharmacodynamics between NovoLog and regular human insulin are not associated with differences in overall glycemic control.

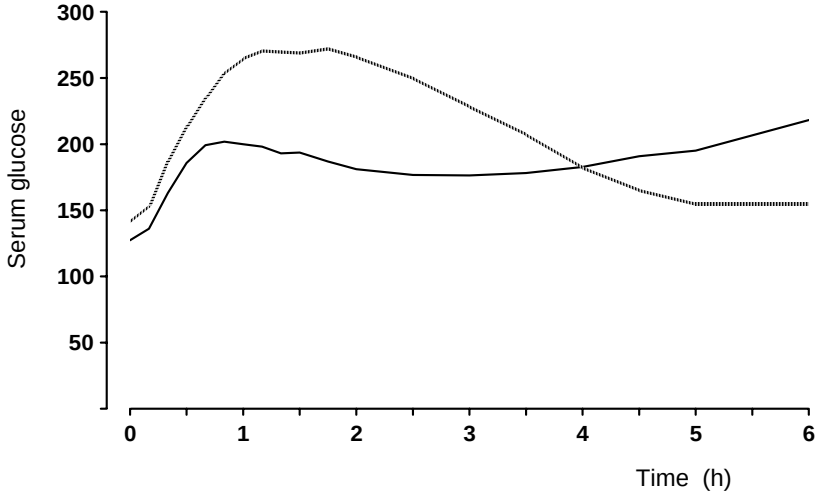


Figure 3. Serial mean serum glucose collected up to 6 hours following a single pre-meal dose of NovoLog (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with Type 1 diabetes.
A double-blind, randomized, two-way cross-over study with 16 patients 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 (see Figure 4).

Time (h)

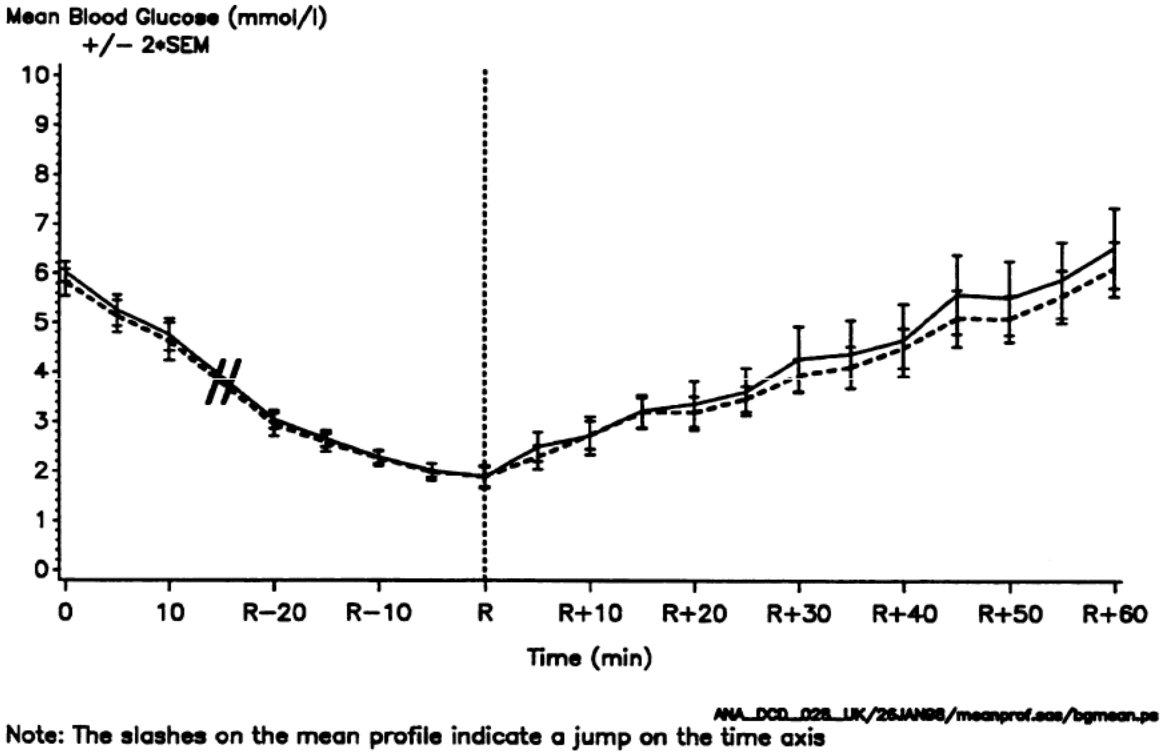


Figure 4. Mean blood glucose profiles following intravenous infusion of NovoLog (hatched curve) and regular human insulin (solid curve) in 16 patients with Type 1 diabetes. R represents the time of autonomic reaction.

Special 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.

Geriatrics - The effect of age on the pharmacokinetics and pharmacodynamics of NovoLog has not been studied.

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 HbAlc) between genders in a trial in patients with Type 1 diabetes.

Obesity - 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 Cmax, of NovoLog were generally unaffected by BMI. Clearance of NovoLog was reduced by 28% in patients with BMI

>32 compared to patients with BMI <23 when a single dose of 0.1 U/kg NovoLog was administered. However, only 3 patients with BMI <23 were studied.

Ethnic Origin - The effect of ethnic origin on the pharmacokinetics of NovoLog has not been studied.

Renal Impairment - Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. A single subcutaneous dose of NovoLog was administered in a study of 18 patients with creatinine clearance values ranging from normal to <30 mL/min and not requiring hemodialysis. No apparent effect of creatinine clearance values on AUC and Cmax of NovoLog was found. However, only 2 patients with severe renal impairment were studied (<30 mL/min). Careful glucose monitoring and dose adjustments of insulin, including NovoLog, may be necessary in patients with renal dysfunction (see PRECAUTIONS, Renal Impairment).

Hepatic Impairment - Some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. In an open-label, single-dose study of 24 patients with Child-Pugh Scores ranging from 0 (healthy volunteers) to 12 (severe hepatic impairment), no correlation 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 PRECAUTIONS, Hepatic Impairment).

Pregnancy - The effect of pregnancy on the pharmacokinetics and pharmacodynamics of NovoLog has not been studied (see PRECAUTIONS, Pregnancy).

Smoking - The effect of smoking on the pharmacokinetics/pharmacodynamics of NovoLog has not been studied.

CLINICAL STUDIES

To evaluate the safety and efficacy of NovoLog in patients with Type 1 diabetes, two six-month, open-label, active-control (NovoLog vs. Novolin® R) studies were conducted (see Table 1). 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 HbA1c, the rates of hypoglycemia (as determined from the number of events requiring intervention from a third party), and the incidence of ketosis were clinically comparable for the two treatment regimens. The mean total daily doses of insulin were greater (1-3 U/day) in the NovoLog-treated patients compared to patients who received regular human insulin. This difference was primarily due to basal insulin requirements. No serum glucose measurements were obtained in these studies.

To evaluate the safety and efficacy of NovoLog in patients with Type 2 diabetes, one six-month, open-label, active-control (NovoLog vs. Novolin R) study was conducted (see Table 1). 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 HbAlc and the rates of hypoglycemia (as determined from the number of events requiring intervention from a third party) were clinically comparable for the two treatment regimens.

Table 1. Results of two six-month, active-control, open-label trials in patients with Type 1 diabetes (Studies A and B) and one six-month, active-control, open-label trial in patients with Type 2 diabetes (Study C).

Study	Treatment (n)	Mean HbA1c (%)		Hypoglycemia[1] (events / month / patient)	% of Patients Using Various Numbers of Insulin Injections / Day[2]				
		Baseline	Month 6		Rapid-acting			Basal	
					1 - 2	3	4 - 5	1	2
A	NovoLog (n=694)	8.0	7.9	0.06	3	75	22	54	46
	Novolin R (n=346)	8.0	8.0	0.06	6	75	19	63	37
B	NovoLog (n=573)	7.9	7.8	0.08	4	90	6	94	6
	Novolin R (n=272)	8.0	7.9	0.06	4	91	4	93	7
C	NovoLog (n=90)	8.1	7.7	0.02	4	93	4	97	4
	Novolin R (n=86)	7.8	7.8	0.01	2	93	5	93	7

[1] Events requiring intervention from a third party during the last three months of treatment
[2] Percentages are rounded to the nearest whole number

To evaluate the use of NovoLog by subcutaneous infusion with an external pump, two open-label, parallel design studies (6 weeks [n=29] and 16 weeks [n=118]) compared NovoLog versus Velosulin (buffered regular human insulin) in patients with Type 1 diabetes. Changes in HbA1c and rates of hypoglycemia were comparable. Patients with Type 2 diabetes were also studied in an open-label, parallel design trial (16 weeks [n=127]) using NovoLog by subcutaneous infusion compared to pre-prandial injection (in conjunction with basal NPH injections). Reductions in HbA1c and rates of hypoglycemia were comparable. (See INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, Mixing of Insulins, Information for Patients, DOSAGE AND ADMINISTRATION, and RECOMMENDED STORAGE.)

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

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

WARNINGS

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

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

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

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

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

PRECAUTIONS

General

Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated with the use of all insulins. Because of differences in the action of NovoLog and other insulins, care should be taken in patients in whom such potential side effects might be clinically relevant (e.g., patients who are fasting, have autonomic neuropathy, or are using potassium-lowering drugs or patients taking drugs sensitive to serum potassium level). Insulin stimulates potassium movement into the cells, possibly leading to hypokalemia that left untreated may cause respiratory paralysis, ventricular arrhythmia, and death. Since intravenously administered

insulin has a rapid onset of action, increased attention to hypoglycemia and hypokalemia is necessary. Therefore, glucose and potassium levels must be monitored closely when NovoLog or any other insulin is administered intravenously. Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated with the use of all insulins. As with all insulin preparations, the time course of NovoLog action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity. Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan. Insulin requirements may be altered during illness, emotional disturbances, or other stresses.

Hypoglycemia - As with all insulin preparations, hypoglycemic reactions may be associated with the administration of NovoLog. Rapid changes in serum glucose levels may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control (see PRECAUTIONS, Drug Interactions). Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to patients' awareness of hypoglycemia.

Renal Impairment - As with other insulins, the dose requirements for NovoLog may be reduced in patients with renal impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Hepatic Impairment - As with other insulins, the dose requirements for NovoLog may be reduced in patients with hepatic impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Allergy - Local Allergy - As with other insulin therapy, patients may experience redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of NovoLog. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.
Systemic Allergy - Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life threatening.
Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient.
In controlled clinical trials using injection therapy, allergic reactions were reported in 3 of 735 patients (0.4%) who received regular human insulin and 10 of 1394 patients (0.7%) who received NovoLog. During these and other trials, 3 of 2341 patients treated with NovoLog were discontinued due to allergic reactions.

Antibody Production - Increases in levels of anti-insulin antibodies that react with both human insulin and insulin aspart have been observed in patients treated with NovoLog. The number of patients treated with insulin aspart experiencing these increases is greater than the number

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

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

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

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

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

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

Information for Patients

For all patients:
Patients should be informed about potential risks and advantages of NovoLog therapy including the possible side effects. 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.

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

For 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 Disetronic H-TRON series, MiniMed 500 series and other equivalent pumps

Reservoirs and infusion sets:
NovoLog is recommended for use in any reservoir and infusion sets that are compatible with insulin and the specific pump. 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 WARNINGS, PRECAUTIONS, Mixing of Insulins, DOSAGE AND ADMINISTRATION, and RECOMMENDED STORAGE.)

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

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

- The following are examples of substances that may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetic products, ACE inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), sulfonamide antibiotics.
- The following are examples of substances that may reduce the blood-glucose-lowering effect: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, salbutamol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives).
- Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
- In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent (see CLINICAL PHARMACOLOGY).

Mixing of Insulins

- A clinical study in healthy male volunteers (n=24) demonstrated that mixing NovoLog with NPH human insulin immediately before injection produced some attenuation in the peak concentration of NovoLog, but that the time to peak and the total bioavailability of NovoLog were not significantly affected. If NovoLog is mixed with NPH human insulin, NovoLog should be drawn into the syringe first. The injection should be made immediately after mixing. Because there are no data on the compatibility of NovoLog and crystalline zinc insulin preparations, NovoLog should not be mixed with these preparations.
- The effects of mixing NovoLog with insulins of animal source or insulin preparations produced by other manufacturers have not been studied (see WARNINGS).
- Mixtures should not be administered intravenously.
- **When used in external subcutaneous infusion pumps for insulin, NovoLog should not be mixed with any other insulins or diluent.**

Carcinogenicity, Mutagenicity, Impairment of Fertility

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

Pregnancy - Teratogenic Effects - Pregnancy Category C

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

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

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

Of the total number of patients (n= 1,375) treated with NovoLog in 3 human insulin-controlled clinical studies, 2.6% (n=36) were 65 years of age or over. Half of these patients had Type 1 diabetes (18/1285) and half had Type 2 (18/90) diabetes. The HbA1c response to NovoLog, as compared to human insulin, did not differ by age, particularly in patients with Type 2 diabetes.

Additional studies in larger populations of patients 65 years of age or over are needed to permit conclusions regarding the safety of NovoLog in elderly compared to younger patients. Pharmacokinetic/pharmacodynamic studies to assess the effect of age on the onset of NovoLog action have not been performed.

ADVERSE REACTIONS

Clinical trials comparing NovoLog with regular human insulin did not demonstrate a difference in frequency of adverse events between the two treatments.
Adverse events commonly associated with human insulin therapy include the following:
Body as Whole - *Allergic reactions* (see PRECAUTIONS, Allergy).
Skin and Appendages - *Injection site reaction, lipodystrophy, pruritus, rash* (see PRECAUTIONS, Allergy; Information for Patients, Usage in Pumps).
Other – *Hypoglycemia, Hyperglycemia and ketosis* (see WARNINGS and PRECAUTIONS).
In controlled clinical trials, small, but persistent elevations in alkaline phosphatase result were observed in some patients treated with NovoLog. The clinical significance of this finding is unknown.

OVERDOSAGE

Excess insulin may cause hypoglycemia and hypokalemia, particularly during IV administration. Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

DOSAGE AND ADMINISTRATION

NovoLog should generally be given immediately before a meal (start of meal within 5 to10 minutes after injection) because of its fast onset of action. The dosage of
NovoLog should be individualized and determined, based on the physician's advice, in accordance with the needs of the patient. The total daily insulin requirement may vary and is usually between 0.5 to1.0 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.
When used in external insulin infusion pumps, the initial programming of the pump is based on the total daily insulin dose of the previous regimen. Although there is significant interpatient variability, approximately 50% of the total dose is given as meal-related boluses of NovoLog and the remainder as basal infusion. Additional basal insulin injections, or higher basal rates in external subcutaneous infusion pumps may be necessary. **NovoLog in the reservoir and infusion sets, and the injection site must be changed at least every 48 hours.**

NovoLog should be administered by subcutaneous injection in the abdominal wall, the thigh, or the upper arm, or by continuous subcutaneous infusion in the abdominal wall. Injection sites and infusion sites should be rotated within the same region. As with all insulins, the duration of action will vary according to the dose, injection site, blood flow, temperature, and level of physical activity.
Intravenous administration of NovoLog is possible under medical supervision with close monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia. For intravenous use, NovoLog should be used at concentrations from 0.05 U/mL to 1.0 U/mL insulin aspart in infusion systems with the infusion fluids 0.9% sodium chloride, 5% dextrose, or 10% dextrose with 40 mmol/l potassium chloride using polypropylene infusion bags.
NovoLog may be diluted with Insulin Diluting Medium for NovoLog to a concentration of 1:10 (equivalent to U-10) or 1:2 (equivalent to U-50).
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Never use any NovoLog if it has become viscous (thickened) or cloudy; use it only if it is clear and colorless. NovoLog should not be used after the printed expiration date.

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®, and NovoFine® disposable needles.

RECOMMENDED STORAGE
NovoLog in unopened vials, cartridges, and NovoLog FlexPen Prefilled syringes should be stored between 2° and 8°C (36° to 46°F). *Do not freeze.* **Do not use NovoLog if it has been frozen or exposed to temperatures that exceed 37°C (98.6°F).** After a vial, cartridge, or Prefilled syringe has been punctured, it 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. Cartridges should not be refrigerated after insertion into the Novo Nordisk 3 mL PenFill cartridge compatible insulin delivery devices. The infusion set (tubing and needle) should be changed at least every 48 hours.

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

	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	28 days	Until expiration date	28 days **(Do not refrigerate)**

Infusion bags prepared as indicated under DOSAGE AND ADMINISTRATION are stable at room temperature for 24 hours. A certain amount of insulin will be initially adsorbed to the material of the infusion bag.

NovoLog diluted with Insulin Diluting Medium for NovoLog may remain in patient use at temperatures below 30°C (86°F) for 28 days.

Rx only

Date of Issue: XXXX
8-XXXX-XX-XXX-X

Manufactured For Novo Nordisk Inc., Princeton, New Jersey 08540
Manufactured By Novo Nordisk A/S, 2880 Bagsvaerd, Denmark

www.novonordisk-us.com

Exp. Date/Control:

Insulin Diluting Medium for NovoLog®

10 mL

Use only with Novolog®

Store between 2°C and 8°C (36° - 46°F). Protect from light.

NDC xxxx-xxxx-x

This product does not contain insulin.

Novo Nordisk Inc.
Princeton, NJ 08540
Manufactured by
Novo Nordisk A/S
2880 Bagsvaerd, Denmark

For information contact:
Novo Nordisk Inc.
Princeton, NJ 08540

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

Barcode

Exp. Date/
Control:

22-190-26

1 mL Diluting Medium contains Glycerol, Disodium Phosphate Dihydrate, m-Cresol 1.5 mg, Phenol 0.65 mg, Sodium Hydroxide, Hydrochloric Acid and Water for Injections

10 mL

Insulin Diluting Medium for NovoLog®

List XXXXXX NDC XXXX-XXXX-XX

Insulin Diluting Medium for NovoLog®

10 mL

Use only with NovoLog®

8-0749-31-301-X

CAUTION: For use by health professionals only to dilute Novo Nordisk insulin products. Dilutions should be performed under aseptic conditions. Store unused vials at 2°C - 8°C (36° - 46°F) and protect from light and heat - do not freeze.

Do not use the diluting medium if it does not appear water-clear and colorless or if the cap is loose or missing. The diluted insulin preparation should not be mixed with other insulin preparations in the same syringe.

Do not use the diluting medium in insulin pumps. Never use diluting medium after the expiration date printed on the box or vial label.

Keep out of reach of children.

This product does not contain insulin.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020986/S-040

CHEMISTRY REVIEW(S)

DIVISION OF POST-MARKETING VALUATION
Review of Chemistry, Manufacturing, and Controls

NDA # 20-986 **SUPPLEMENT**: SCM-040 **REVIEW** # 2 REVIEW DATE: 27-Oct-2006

SUPPLEMENT(S) PROVIDE(S) FOR: addition of an insulin diluting medium to be used with NovoLog.

TYPE of SUPPLEMENT:
☐ SUPAC ☐ CBE-0 ☐ CBE-30 xx Prior Approval ☐ Bundled Review ☐ Expedited Review

THE USER FEE GOAL DATE: 29-Oct-2006

SUBMISSION DATE:	**DOC. TYPE**	**CDER DATE**	**ASSIGNED DATE**
29-Jun-2006			18-Aug-2006

SUBMISSION REVIEWED:	**TYPE**	**REVIEW DATE**
Review # 1	CMC information	28-Sep-2006
Review #2	Microbiological Consult	27-Oct-2006

NAME & ADDRESS OF APPLICANT:

Representative: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
Novo Nordisk, Inc.
100 College Road West, Princeton, New Jersey 08540
T: 609-987-5800, F: 609-987-3916

DRUG PRODUCT NAME:

Proprietary:	NovoLog®
Nonproprietary/Established/USAN:	Insulin aspart injection (rDNA origin)
Code Name/#:	
Chem. Type/Therapeutic Class:	1/S

DESI/PATENT STATUS: N/A

PHARMACOL. CATEGORY/INDICATION: Insulins/Treatment of Diabetes Mellitus

DOSAGE FORM:	Parenteral
STRENGTHS:	100 Units/mL, 3 mL
ROUTE OF ADMINISTRATION:	Subcutaneous
DISPENSED:	xx Rx ____ OTC

SUPPORTING DOCUMENTS: N/A
RELATED DOCUMENTS (if applicable): N/A

CONSULTS: Microbiological Review for the (b) (4) sterilization process validation

REMARKS/COMMENTS:

This is an Addendum to this supplement for the recommendation made by Microbiologist Review. A microbiological consult was submitted by Rebecca McKnight, dated 20-Sep-2006 and found Acceptable by Microbiologist, James McVey, dated 27-Oct-2006. Therefore, the recommendation for this supplement from a Chemist standpoint is "Approval".

CONCLUSIONS & RECOMMENDATIONS: **Approval**

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

/s/

Li-Shan Hsieh
10/27/2006 02:59:02 PM
CHEMIST

Jim Vidra
10/27/2006 03:12:12 PM
CHEMIST

DIVISION OF POST-MARKETING VALUATION
Review of Chemistry, Manufacturing, and Controls

NDA # 20-986 **SUPPLEMENT**: SCM-040 REVIEW DATE: 28-Sep-2006

SUPPLEMENT(S) PROVIDE(S) FOR: addition of an insulin diluting medium to be used with NovoLog.

TYPE of SUPPLEMENT:
☐ SUPAC ☐ CBE-0 ☐ CBE-30 ☒ Prior Approval ☐ Bundled Review ☐ Expedited Review

THE USER FEE GOAL DATE: 29-Oct-2006

SUBMISSION DATE	**DOC. TYPE**	**CDER DATE**	**ASSIGNED DATE**
29-Jun-2006			18-Aug-2006

NAME & ADDRESS OF APPLICANT:

Representative: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
Novo Nordisk, Inc.
100 College Road West, Princeton, New Jersey 08540
T: 609-987-5800, F: 609-987-3916

DRUG PRODUCT NAME:

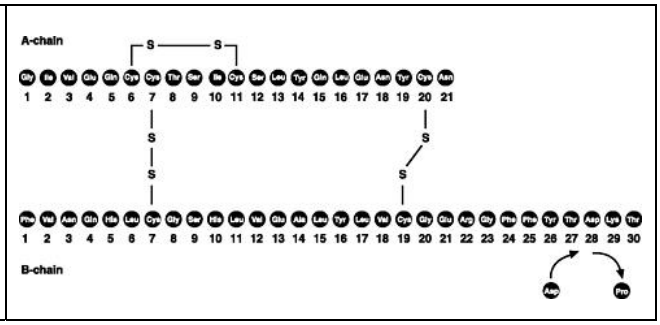
Proprietary:	NovoLog®
Nonproprietary/Established/USAN:	Insulin aspart injection (rDNA origin)
Code Name/#:	
Chem. Type/Therapeutic Class:	1/S

DESI/PATENT STATUS: N/A

PHARMACOL. CATEGORY/INDICATION: Insulins/Treatment of Diabetes Mellitus

DOSAGE FORM:	Parenteral
STRENGTHS:	100 Units/mL, 3 mL
ROUTE OF ADMINISTRATION:	Subcutaneous
DISPENSED:	xx Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA(M.F.), MOLECULAR WEIGHT(M.W.):

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) 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.	

SUPPORTING DOCUMENTS: N/A

RELATED DOCUMENTS (if applicable): N/A

CONSULTS: N/A

REMARKS/COMMENTS: (see review notes as well)

The proposed addition of diluent to be used in the insulin product has been reviewed. The manufacturing for this diuent is found to be acceptable based on the following: (1) the composition of diluent does not affect the isotonicity of NovoLog (2) the manufacturing process has been validated, (3) the storage conditions for this diluent is supported with adequate stability data, and (5) Overall recommendation made by the Office of Compliance for this facility is Acceptable. Therefore, the recommendation for this supplement from a Chemist standpoint is "Approval".

CONCLUSIONS & RECOMMENDATIONS: **Approval**

Li-Shan Hsieh, Ph.D., Review Chemist,

James Vidra, Ph.D., Chief of Branch VII

Review Notes

This submission is for addition of an insulin diluting medium to be used with NovoLog.

Composition and Components of Insulin diluting medium:

Table 1 Composition of Insulin diluting medium 10 mL

Name	Quantity	Function	Reference to standards
Glycerol	(b) (4)	(b) (4)	(b) (4)
Phenol[1]	0.65 mg		
Metacresol[1]	1.5 mg	Preservative	
Disodium Phosphate, Dihydrate	(b) (4)	(b) (4)	
Sodium Hydroxide 2N	(b) (4)	(b) (4)	
Hydrochloric Acid 2N			
Water for Injections			

(b) (4)

Batch formula

Table 1 Insulin diluting medium 10 ml

Solution	Name of Ingredient	Amount	Quality Standards
I	(b) (4)	(b) (4)	
	Glycerol		
	Metacresol[1]		
	Phenol[1]		
	Disodium Phosphate Dihydrate		
	Hydrochloric Acid (b) (4)		
	Water for Injections		

(b) (4)

(b) (4)

(b) (4)

Table 2 Comparison of compositions

Function	Ingredient	Insulin Diluting Medium	Undiluted NovoLog 100 U/mL	NovoLog Diluted to 50 U/mL	NovoLog Diluted to 10 U/mL
Active substance	Insulin aspart	-	100 units (b) (4) (b) (4)	50 units (b) (4) (b) (4)	10 units (b) (4) (b) (4)
(b) (4)	Glycerol	(b) (4)	16 mg	(b) (4)	(b) (4)
(b) (4)	Phenol	0.65 mg	1.5 mg	1.08 mg	0.74 mg
Preservative	Metacresol	1.5 mg	1.72 mg	1.61 mg	1.52 mg
(b) (4) (b) (4)	Zinc	-	19.6 µg (b) (4) (b) (4)	9.8 µg (b) (4) (b) (4)	1.96 µg (b) (4) (b) (4)
(b) (4) (b) (4)	Sodium chloride	-	0.58 mg	0.29 mg	0.06 mg
(b) (4) (b) (4)	Disodium phosphate, dihydrate	(b) (4)	1.25 mg	(b) (4)	(b) (4)
(b) (4)	Water for Injection	(b) (4)			
	pH	(b) (4)	7.2 – 7.6	(b) (4)	(b)

Novo Nordisk® Pharmaceutical Industries, Inc., Clayton, North Carolina.

On a qualitative basis, the only differences between the diluent and undiluted NovoLog are the presence of ***sodium chloride*** *and* ***zinc*** *in the NovoLog formulation.* (b) (4) *As indicated in the chart, the different concentrations of NovoLog have the same zinc-to-insulin aspart ratio as in the undiluted NovoLog. It appears that the composition of the diluent is justified and is* ***acceptable****.*

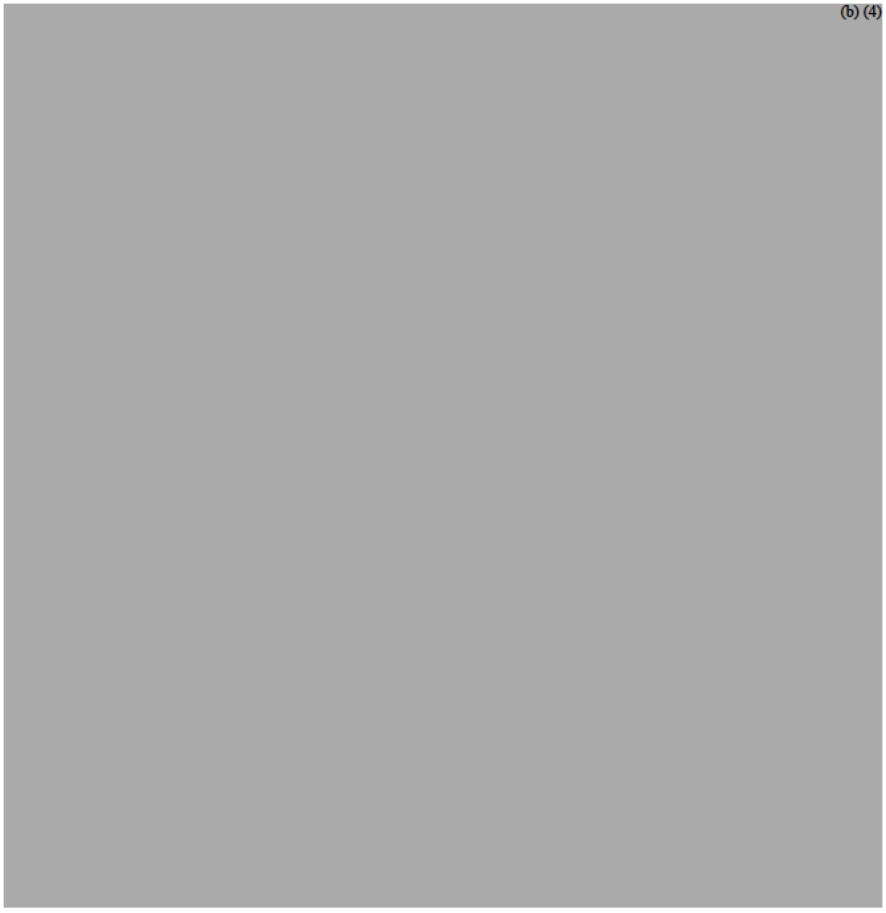
Manufacturer:
Building 2H/2HM at Novo Nordisk A/S in Bagsværd, Denmark

Note*: The Bagsvard site is currently approved for manufacturing NovoLog®, 10 mL vial presentation. This site was recently inspected during 28-Sep-2004 to 01-Oct-2004 and was found acceptable under profile SVS. The Office of Compliance recommended Acceptable on 23-Jan-2006 (see ATTACHMENT of this review).*

Manufacturing process
The manufacturing process and controls are illustrated in Figure 1 below.

Figure 1 Flow Diagram for Insulin Diluting Medium, 10mL

Figure 1 Flow Diagram for Insulin Diluting Medium, 10mL (continued)



As no active drug substance is included in the diluent, the (b) (4) . The critical steps (b) (4) for Insulin diluting medium 10 ml are listed below.

(b) (4)

Control of Drug Product - diluent
The release specifications for the diluent are available shown below

(b) (4)

Certificates of analyses for two production scale batches Batch RQ50027 and batch RQ50668 are provided in 3.2.P.5.4 of the submission and complied with the proposed specifications. ***Adequate***

Process validation

(b) (4) . This means that the validation described in enclosures is also valid for Insulin Diluting Medium. *A micro consult was submitted by Rebecca McKnight, dated 20-Sep-2006. This is* ***adequate***.

Container Closure System

(b) (4)

. ***This vials meet the requirements for Injectables in*** (b) (4) ***and are adequate***.

Stability
Section 2.3.P.8.1 of the submission summarizes the four stability studies performed for the diluent and NovoLogdiluted to 10 U/mL and 50 U/mL.

Based upon the results of the reported studies, the recommended shelf-life for the diluent is

24 months of storage at 5°C.

When NovoLog is diluted to down to a 10 U/mL, the unused diluted product may be stored up to

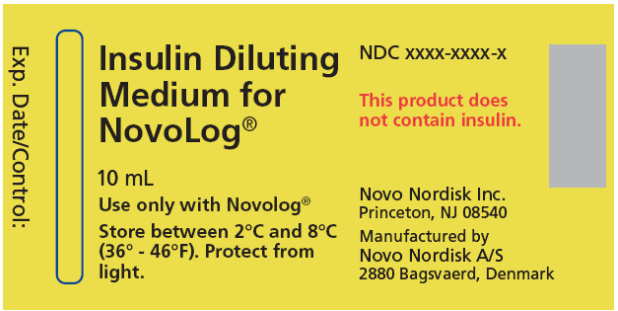
8 weeks at 5°C± 3°C protected from light.

An **in-use time of 28 days** is recommended for the diluted NovoLog when stored at temperatures **not above 30°C**.

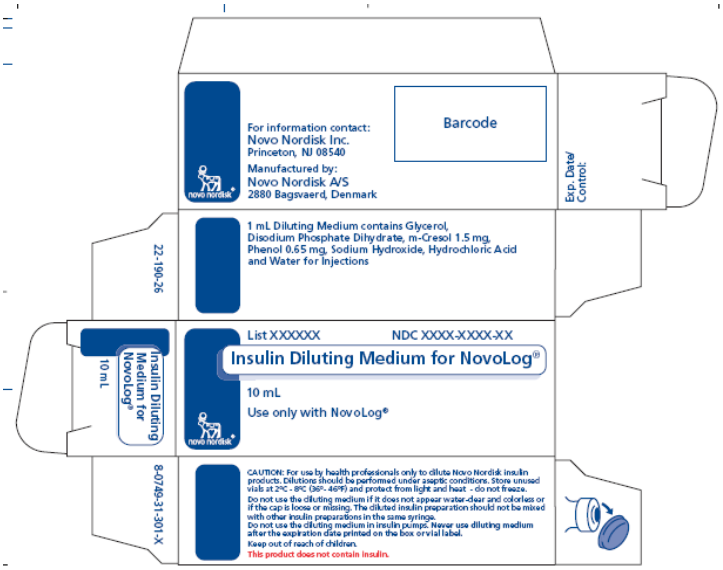
10 mL samples of NovoLog diluted to 50 U/mL and 10 U/mL concentrations were stored horizontally and protected from light for 3 months at 5°C and 25°C. A white fiber-like particle was seen in one sample of 50 U/mL NovoLog stored at 5°C, however, no particles appeared in the physical stability test which was conducted under worst case conditions (shaking while stored at 37°C). This suggests that the observed particle was a random occurrence and diluted NovoLog is stable for up to 3 months when stored at 5°C. Samples of NovoLog at 100 U/mL strength and diluted to 50 U/mL and 10 U/mL concentrations were exposed to 37°C with shaking (worst case conditions). These were followed for time to fibrillation. No significant differences were seen among the diluted NovoLog solutions compared to the undiluted NovoLog. It can be concluded that the diluent does not significantly affect the physical stability of the product. An in-use test was performed on two batches of diluted NovoLog, 10 U/mL to establish the in-use time for the product. The test batches were prepared from samples of two production scale batches of NovoLog and two pilot scale batches of diluent. The partially-filled vials of diluted NovoLog were stored horizontally at 30°C ± 2°C and subjected to needle penetrations and turnings. The results support an in-use time of 28 days at temperatures not above 30°C ± 2°C for NovoLog diluted down to 10 U/mL with Insulin Diluting Medium. Three production scale batches (250 L) of diluent stored for 30 months at 5°C ambient humidity and for 12 months at 25°C ambient humidity were examined for macroscopy, pH, phenol, metacresol, sterility, and preservative efficacy. One batch showed fluctuations in the preservative levels which was attributed to the use of a slightly different closure ((b) (4)*) for that batch. Tests for sterility and preservative efficacy were performed until 24 months of storage. Based on the results, the batches were stable during 24 months storage at 2-8 °C overall. This is* ***adequate to support the proposed expiry***.

Labeling:

(1) Diluent medium container



(2) Diluent medium carton



(3) Package insert

Proposed addition is added in red color.
Lines 507-508 under Dosage and Administration
NovoLog may be diluted with Insulin Diluting Medium for NovoLog to a concentration of 1:10 (equivalent to U-10) or 1:2 (equivalent to U-50).

Line 542-543 under Recommended Storage
NovoLog diluted with Insulin Diluting Medium for NovoLog may remain in patient use at temperatures below 30°C (86°F) for 28 days.

The proposed labeling for container and Carton appears appropriate for their content, name, manufacturer, lot #, storage conditions, and warning for not containing insulin. ***Adequate***

Environmental Assessment

A categorical exclusion from environmental assessment for the drug products, insulin aspart (NovoLog®), is requested based 21 CFR 25.31b, based on entry into the aquatic environment is below 1 part per billion (1 ppb). The estimated EIC for insulin aspart is (b) (4) ppb. ***Adequate***

ATTACHMENT

•(s0P•&k4S•&17.27c66F 23-FEB-2006 FDA CDER EES
Page 1 of 1

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 20986/ (b) (4)	Action Goal:	
Stamp:	16-DEC-2005	District Goal:	12-MAY-2006
Regulatory Due:	16-JUN-2006	Brand Name:	NOVOLOG
Applicant:	NOVO NORDISK INC	Estab. Name:	
	100 COLLEGE RD WEST	Generic Name:	INSULIN ASPART
	PRINCETOWN, NJ 08540		RECOMBINANT
Priority:	1S	Dosage Form:	(INJECTION)
Org Code:	510	Strength:	100 U/ML

Application Comment: ALTERNATE MANUFACTURING SITE FOR NOVOLOG DRUG PRODUCT, 3 ML CARTRIDGE PENFILL (on 18-JAN-2006 by J. BROWN (HFM-71) 301-827-1296)

FDA Contacts: T. BOUIE 301-796-1649 , Project Manager
J. BROWN 301-796-1652 , Team Leader

Overall Recommendation: ACCEPTABLE on 23-JAN-2006by J. D AMBROGIO(HFD-322)301-827-9049

Establishment: CFN 1058438 FEI 1000158576
NOVO NORDISK PHARMACEUTICAL INDUSTRIES INC
3612 POWHATAN RD
CLAYTON, NC 27520

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: SVS OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	18-JAN-2006				BROWNJA
SUBMITTED TO DO	18-JAN-2006	10D			DAMBROGIOJ
DO RECOMMENDATION	20-JAN-2006			ACCEPTABLE BASED ON FILE REVIEW	MWOLESKE

A GMP INSPECTION WAS CONDUCTED 9/28-10/1/2004 AND CLASSIFIED NAI. (b) (4) [redacted]. PROFILE CLASS WAS SVS WAS JUDGED ACCEPTABLE.

OC RECOMMENDATION	23-JAN-2006			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

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

/s/

Li-Shan Hsieh
10/19/2006 05:01:39 AM
CHEMIST

Jim Vidra
10/19/2006 09:17:48 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020986/S-040

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

27 October 2006

NDA: 20-986 SCS-040

Drug Product Name
Proprietary: Novolog
Non-proprietary: Insulin Aspartate Injection
Drug Product Priority Classification: hormone diluent

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
29 June 2006	29 June 2006	18 Sept. 2006	26 Sept. 2006

Submission History (for amendments only) N.A.

Applicant/Sponsor

Name:	Novo Nordisk
Address:	Bagsvaerd, Denmark
Representative:	Elizabeth L. Tan, Ph.D.
Telephone:	(609) 987-5940

Name of Reviewer: James L. McVey

Conclusion: Recommended for approval from Product Quality Microbiology perspective.

Product Quality Microbiology Data Sheet

A. **1.** **TYPE OF SUBMISSION:** Prior Approval Supplement

2. **SUBMISSION PROVIDES FOR:** Manufacturing and distributing a diluent for Novolog.

3. **MANUFACTURING SITE:** Bagsvaerd, Denmark

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** NovoLog diluted to 10 U/mL and 50 U/mL. The dilution is due to the small body weight and size of children patients.

5. **METHOD(S) OF STERILIZATION:** (b) (4).

6. **PHARMACOLOGICAL CATEGORY:** Hormone.

B. **SUPPORTING/RELATED DOCUMENTS:** NDA 20-986 for NovoLog and supplement 033 approved on September 13, 2005 for pediatric indications.

C. **REMARKS:** Due to the small volumes, that would be difficult to administer with existing commercially available syringes, a diluent is needed for application of pediatric doses. This supplement describes the manufacture and labeling of Insulin Diluting Medium for NovoLog.

Filename: N20986s040r1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Approve

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - None.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - The diluent is (b) (4)

B. Brief Description of Microbiology Deficiencies - None.

C. Assessment of Risk Due to Microbiology Deficiencies - No added risk due to the implementation of this supplement.

III. Administrative

A. Reviewer's Signature _____
James L. McVey

B. Endorsement Block

_____
Stephen Langille

C. CC Block . DFS

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE N.A.

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product – The diluent formulation is similar to NovoLog except that it does not contain insulin, Zinc or NaCl. See Table 2 below.

Table 2 Comparison of compositions

Function	Ingredient	Insulin Diluting Medium	Undiluted NovoLog 100 U/mL	NovoLog Diluted to 50 U/mL	NovoLog Diluted to 10 U/mL
Active substance	Insulin aspart	-	100 units (b) (4) (b) (4)	50 units (b) (4) (b) (4)	10 units (b) (4) (b) (4)
(b) (4)	Glycerol	(b) (4)	16 mg	(b) (4)	(b) (4)
(b) (4)	Phenol	0.65 mg	1.5 mg	1.08 mg	0.74 mg
Preservative	Metacresol	1.5 mg	1.72 mg	1.61 mg	1.52 mg
(b) (4) (b) (4)	Zinc	-	19.6 µg (b) (4) (b) (4)	9.8 µg (b) (4) (b) (4)	1.96 µg (b) (4) (b) (4)
(b) (4) (b) (4)	Sodium chloride	-	0.58 mg	0.29 mg	0.06 mg
(b) (4) (b) (4)	Disodium phosphate, dihydrate	(b) (4)	1.25 mg	(b) (4)	(b) (4)
(b) (4)	Water for Injection	(b) (4)	(b) (4)		
	pH	(b) (4)	7.2 – 7.6	(b) (4)	(b) (4)

- Description of container closure system – A (b) (4)

P.2 Pharmaceutical Development. Not Applicable

P.2.5 Microbiological Attributes

- Container-Closure and Package integrity Section 3.2.P.3.5. page 147 (b) (4)

(b) (4)

Acceptable

- Preservative Effectiveness - The diluent contains (b) (4) Metacresol as antimicrobial preservatives. A preservative effectiveness test for the highest dilution of product was done as part of the stability studies and the results conformed to (b) (4). No data summaries were found.

Acceptable

P.3 Manufacture

P.3.1 Manufacturers.

The drug product diluent is formulated, filled, inspected and labeled at:

Novo Nordisk A.S.
Novo Allo
DK-2880 Bagwood

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

.

(b) (4)

- Building and facilities – Floor plans with air quality classifications are provided for Buildings 2H and 2HM in 3.2.A.1 of the application. These plans are difficult to read because of the small size and loss of definition when electronically expanded. The description is adequate however. The (b) (4) . Equipment is identified on this same diagram but also described in the text along with room locations. (b) (4) which identifies the procedure, equipment and locations of the equipment.
- Overall manufacturing operation – The diluent is formulated in (b) (4)

(b) (4)

and is said to be covered by the media fill data.

- Validation for the (b) (4)

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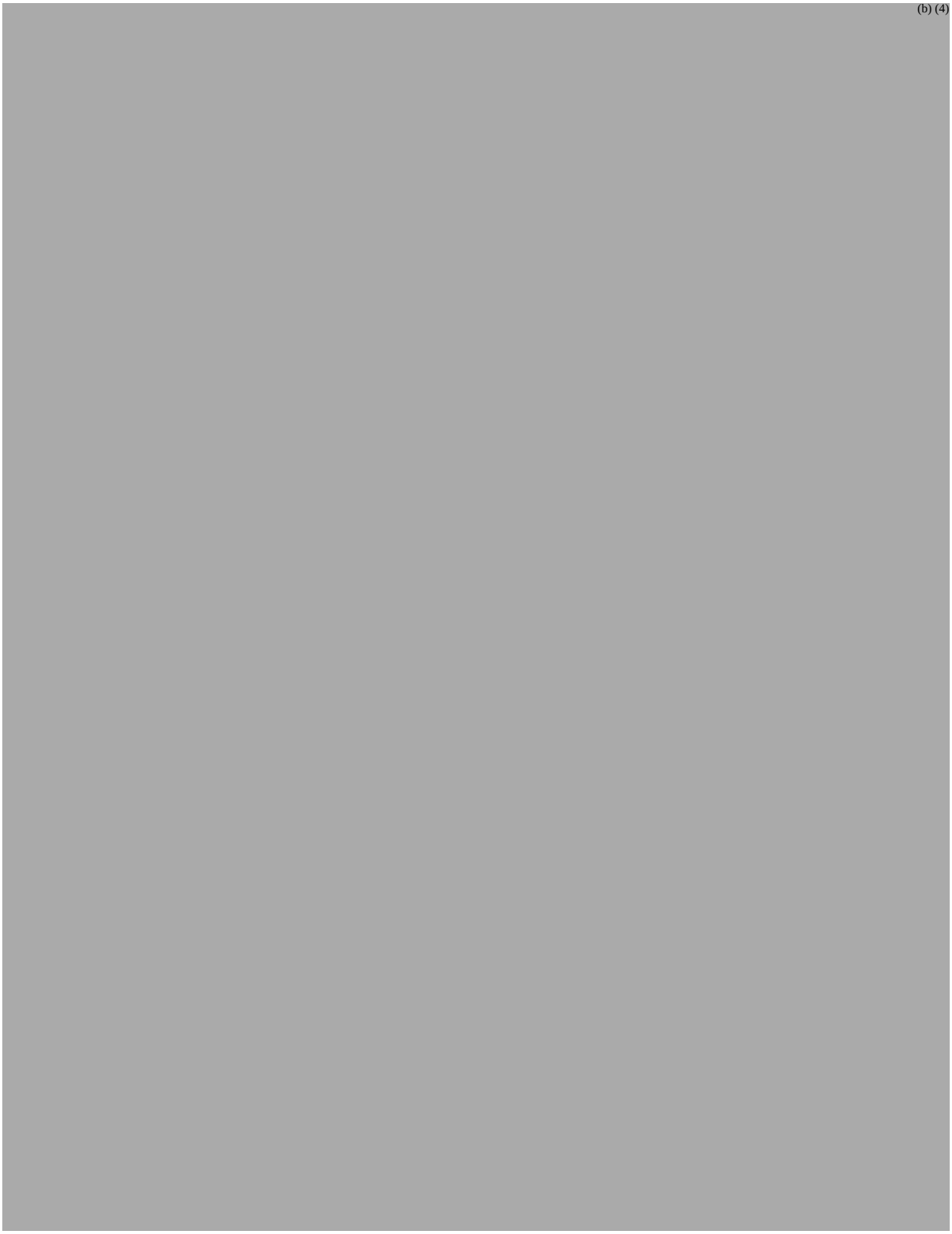
Acceptable

(b) (4)

(b) (4)



All criteria were met.

Acceptable

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P.8 Stability

P.8.1 Stability Summary and Conclusion

MAINTENANCE OF MICROBIOLOGICAL CONTROL AND QUALITY: STABILITY CONSIDERATIONS

- Four studies were conducted to evaluate the stability of the diluting medium. (3.2.P.8.1.)
  - (b) (4) Stability of 10 mL volume after 12 months at 25 C and 30 months at 4 °C.
  - (b) (4) Diluted Insulin 10 U/mL
  - (b) (4) Dilution study
  - (b) (4) Test of 10 U/Ml stability to heat and shaking.

When the diluted product was stored horizontally for 3 months at 5°C and at 25 °C it remained within the acceptable range. No difference was seen between diluted insulin and undiluted insulin in the physical stress testing.

The in-use test was performed for 28 days at 30°C ± 2°C testing the physical, chemical and microbial in-use stability of insulin aspart. During the in-use test the test samples are half-emptied and subjected to manually turning of the vials and penetration of the (b) (4). The following parameters have been tested during the study: Macroscopy, Assay of insulin aspart, (b) (4) insulin aspart, (b) (4), Insulin aspart related impurities, High Molecular Weight Proteins, pH, Zinc, Phenol, Metacresol and Preservative Efficacy. One of the two batches were tested for preservative efficacy and complied with (b) (4) at start and end of the study. The conclusion reached is that the in use time of 28 days at temperatures below 30°C after storage for a maximum of 8 weeks a 5°C ± 3 °C is proposed for insulin aspart diluted down to 10 U/mL with Insuling Diluting Medium. Based on the results evaluated in this report, the batches were stable during 30 months storage at 2-8 °C however test for sterility and preservative efficacy was only tested until 24 months of storage.

Conclusion: Insulin Diluting medium can be stored for 24 months at 5 °C. The diluted products can be stored at 5 °C for 8 weeks away from light with an in-use time of 28 days at temperatures ≤ 30 °C.

Acceptable

P.8.2 Post-Approval Stability Protocol and Stability Commitment. List as N.A. in the Table of Contents.

P.8.3 Stability Data See above.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation . Not done.

A.2.1 Materials of Biological Origin N.A.

A.2.2 Testing at Appropriate Stages of Production N.A.

A.2.3 Viral Testing of Unprocessed Bulk N.A.

A.2.4 Viral Clearance Studies N.A.

R REGIONAL INFORMATION

R.1 Executed Batch Record . An executed batch record was provided. Not reviewed.

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT – N.A.

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS: None.

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

/s/

James McVey
10/27/2006 01:25:12 PM
MICROBIOLOGIST

Stephen Langille
10/27/2006 01:38:10 PM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020986/S-040

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-986/S-040 **PRIOR APPROVAL SUPPLEMENT**

Novo Nordisk, Inc.
Attention: Mary Ann McElligott, PhD
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) Parenteral, 100 units/mL
NDA Number:	20-986
Sequence Number:	040
Date of supplement:	June 29, 2006
Date of receipt:	June 29, 2006

This supplemental application proposes the addition of an insulin diluting medium to be used with the drug product.

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 August 28, 2006 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 29, 2006.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Rebecca McKnight, Regulatory Health Project Manager for Quality, at (301) 796-1765.

Sincerely,

{See appended electronic signature page}

Robert L. Hummel, Sr., DBA, RAC
Regulatory Health Project Manager for Quality
Division of Postmarketing Evaluation
Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

Robert Hummel

8/7/2006 01:10:50 PM