

July 1, 2011

California Public Resources Code Sections 47115-47116:
Required Reporting by Pharmaceutical Manufacturer
Novo Nordisk Inc.

Novo Nordisk is a Danish based health care company and a world leader in diabetes care. Novo Nordisk's North American headquarters are located at 100 College Road West, Princeton, New Jersey, 08540. Novo Nordisk believes that enhanced educational efforts will lead to proper sharps disposal by patients and care givers and avoid costly programs that would require separation of needles and lancets from glass shards, sharp edged can lids, and other household waste capable of causing puncture wounds and lacerations. All of these items must be properly disposed and all household refuse should be handled properly during pick-up and further processing.

Pursuant to the California Public Resources Code Sections 47115-47116, listed below are currently marketed Novo Nordisk products that utilize sharps and the steps we take to ensure safe disposal. The "Product Information" and "Patient Product Information" material available for each product referenced is included within the appendix portion of the report for reference.

Our diabetes portfolio includes the following injectable products:

- Levemir® (insulin detemir [rDNA origin] injection)
- NovoLog® (insulin aspart [rDNA origin] injection)
- NovoLog® (70% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin]) Mix 70/30
- Novolin® R (regular, human insulin injection [recombinant DNA origin] USP)
- Novolin® N (NPH, Human Insulin Isophane Suspension Injection [recombinant DNA origin])
- Victoza® (liraglutide [rDNA origin] injection)

Our Biopharmaceutical portfolio includes the following injectable products:

- Norditropin® (somatropin [rDNA origin] injection)
- NovoSeven® RT (Coagulation Factor VIIa [Recombinant] Room Temperature Stable)

Our delivery systems include (both diabetes and biopharmaceutical):

- FlexPen®
- GlucaGen® HypoKit®
- NovoFine® Needles
- NovoFine® Autocover® Needles
- NovoPen® 3
- NovoPen® Junior
- PenMate®

- FlexPro®

Employee Disposal

All of our field personnel are trained on the safe disposal of products and are authorized to discuss safe disposal with healthcare professionals. Samples and/or devices that are expired or compromised are packaged and returned to Capital Returns Inc., located at 6101 North 64th Street, Milwaukee, WI, for destruction. Capital Returns is a certified medical waste disposal company that processes and destroys returned products.

Patient Returns

In the event a patient has an issue with a Novo Nordisk product, an 800 number is listed on our packaging for consumers to call for information and to report complaints. Patients who wish to return products due to defect can call that number and a customer service representative will register the complaint and then send a special shipping container to the patient. The patient subsequently returns the product to the Novo Nordisk manufacturing site in Clayton, North Carolina for investigation and subsequent destruction. Product that may require more detailed investigation is subsequently shipped to Denmark for additional analysis. A replacement product is then sent out to the patient. Per federal law and regulations, we inform the US Food and Drug Administration (FDA) of all patient reactions and certain product complaints, at a minimum on an annual basis.

General Patient Instruction on Proper Sharps Disposal

Novo Nordisk provides hard copy and electronic educational materials for all of our sharp-using and sharp containing products. These materials include product inserts and product web pages (www.novonordisk-us.com). Proper use and disposal of sharps is covered in these materials.

Novo Nordisk does not provide sharps containers for diabetes products nor do we supply funding to patients and/or other collection groups for the destruction of such materials. However, we do include a sharps container in the pediatric starter kit for Norditropin®. All of our material and literature are reviewed and approved internally, and sent to the FDA for review as per regulations. The material we provide on the use and disposal of sharps is comprehensive and simple to understand.

Diabetes Products and Background on Sharps Disposal Instruction

For patients using Novo Nordisk diabetes products we recommend the use of our NovoFine® and/or Autocover needles for all of our medication delivery systems. The patient literature supplied with these delivery systems illustrates the proper way to use and dispose of needles – that is to remove the cap and dispose of the product according to local and/or municipal regulations. Audio and visual instruction is also available within the company website and other multimedia formats for patients to review in their home or a physician's office. The Patient Package Insert that accompanies the Levemir FlexPen™ contains directions for sharps disposal and can be found in the appendix.

Another example comes from the Package Insert for Levemir® which states:

To avoid needle sticks, do not recap the needle. After each injection, you must remove the needle before replacing the device cap and dispose of the needle in a puncture resistant container. Used syringes, needles, or lancets should be placed in "sharps" containers (such as red biohazard containers), hard plastic containers (such as detergent bottles), or metal containers (such as an empty coffee can). Such containers should be sealed and disposed of properly.

It is important that you use a new needle for each injection. Health care professionals, relatives, and other caregivers should follow general precautionary measures for removal and disposal of needles to eliminate the risk of unintended needle stick.

Novo Nordisk has developed a safety needle – NovoFine® Autocover®. This single-use needle helps prevent accidental needle puncture wounds while retaining all the benefits of other NovoFine® needles, including comfort, consistency, effectiveness, and ease-of-use.

The NovoFine® Autocover® is fitted with a sliding shield. This shield covers the needle before injection, retracts during injection, and then slides back into place to cover the needle again, locking permanently into a shielding position following insulin delivery. Once the needle has been used, the safety lock indicator turns red to indicate that the shield is now locked. This effectively blocks any accidental needle puncture wounds as well as any re-use of the needle.

Additional information on the NovoFine® Autocover® can be found at http://www.novonordisk.com/diabetes/public/needles/novofine_autocover/default.asp

Biopharmaceutical Products and Background on Sharps Disposal Instruction
NovoSeven® RT is a product that is primarily administered in a clinical setting. Patients treated with NovoSeven® RT under the FDA approved indication receive this product for:

1. Bleeding episodes in hemophiliacs with inhibitors to FVIII or FIX; and
2. In patients with acquired hemophilia and to prevent bleeds during surgical interventions or invasive procedures.

Materials related to administration of the product are disposed of according to the appropriate policies and procedures of the dosing institution for the destruction of biological waste.

Norditropin®, a product treating growth hormone deficiency, also uses a pen delivery system, in conjunction with our NovoFine® or Autocover needles. Educational materials and literature for this product illustrate the proper way to use and dispose of needles. For new pediatric patients using Norditropin®, our starter kit does include a sharps container for safe disposal of needles but no additional support is provided for disposition of needles, after receipt of the initial sharps container.

Conclusion

It is not immediately evident to Novo Nordisk what the basis for concerns about needle disposal is based upon. While there is data analyzing the threat of needle sticks in the health care setting, we have seen little data relating to the threat – or perceived threat – in the general public waste stream. In addition, despite efforts to implement programs and educate the public, there is evidence that citizen compliance with proper disposal techniques is poor. Indeed, “proper disposal techniques” may itself be an oxymoron to the extent that the various federal and state agencies responsible for overseeing this activity espouse very different and sometimes contradictory stances (e.g., recapping needles and breaking needles).

To the extent that a significant problem exists, Novo Nordisk believes it is incumbent on the public and private sector to come together to analyze the problem, evaluate the implications, consider the risk/benefit and cost of addressing the issue and join together in an effort to make a difference. This is not something that any one sector can address by itself. Novo Nordisk is committed to participating with the public sector in any such serious endeavor.

APPENDIX (PRODUCT INFORMATION & PATIENT PRODUCT INFORMATION)

LEVEMIR®

(insulin detemir [rDNA origin] injection)

DESCRIPTION

LEVEMIR® (insulin detemir [rDNA origin] injection) is a sterile solution of insulin detemir for use as an injection. Insulin detemir is a long-acting basal insulin analog, with up to 24 hours duration of action, produced by a process that includes expression of recombinant DNA in *Saccharomyces cerevisiae* followed by chemical modification.

Insulin detemir differs from human insulin in that the amino acid threonine in position B30 has been omitted, and a C14 fatty acid chain has been attached to the amino acid B29. Insulin detemir has a molecular formula of $C_{267}H_{402}O_{76}N_{64}S_6$ and a molecular weight of 5916.9. It has the following structure:

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LEVEMIR is a clear, colorless, aqueous, neutral sterile solution. Each milliliter of LEVEMIR contains 100 U (14.2 mg/mL) insulin detemir, 65.4 mcg zinc, 2.06 mg m-cresol, 16.0 mg glycerol, 1.80 mg phenol, 0.89 mg disodium phosphate dihydrate, 1.17 mg sodium chloride, and water for injection. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH. LEVEMIR has a pH of approximately 7.4.

CLINICAL PHARMACOLOGY

Mechanism of Action

The primary activity of insulin detemir is the regulation of glucose metabolism. Insulins, including insulin detemir, exert their specific action through binding to insulin receptors.

Receptor-bound insulin lowers blood glucose by facilitating cellular uptake of glucose into skeletal muscle and fat and by inhibiting the output of glucose from the liver. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis.

Pharmacodynamics

Insulin detemir is a soluble, long-acting basal human insulin analog with a relatively flat action profile. The mean duration of action of insulin detemir ranged from 5.7 hours at the lowest dose to 23.2 hours at the highest dose (sampling period 24 hours).

The prolonged action of LEVEMIR is mediated by the slow systemic absorption of insulin detemir molecules from the injection site due to strong self-association of the drug molecules and albumin binding. Insulin detemir is distributed more slowly to peripheral target tissues since insulin detemir in the bloodstream is highly bound to albumin.

Figure 1 shows glucose infusion rate results from a glucose clamp study in patients with type 1 diabetes.

Figure 1: Activity Profiles in Patients with Type 1 Diabetes in a 24-hour Glucose Clamp Study

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Figure 2 shows glucose infusion rate results from a 16-hour glucose clamp study in patients with type 2 diabetes. The clamp study was terminated at 16 hours according to protocol.

Figure 2: Activity Profiles in Patients with Type 2 Diabetes in a 16-hour Glucose Clamp Study

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For doses in the interval of 0.2 to 0.4 U/kg, LEVEMIR exerts more than 50% of its maximum effect from 3 to 4 hours up to approximately 14 hours after dose administration.

In a glucose clamp study, the overall glucodynamic effect ($AUC_{GIR\ 0-24h}$) [mean mg/kg \pm SD (CV)] of four separate subcutaneous injections in the thigh was 1702.6 ± 489 mg/kg (29%) in the LEVEMIR group and 1922.8 ± 765 mg/kg (40%) for NPH. The clinical

significance of this difference has not been established.

Pharmacokinetics

Absorption

After subcutaneous injection of insulin detemir in healthy subjects and in patients with diabetes, insulin detemir serum concentrations indicated a slower, more prolonged absorption over 24 hours in comparison to NPH human insulin.

Maximum serum concentration (C_{max}) is reached between 6 and 8 hours after administration.

The absolute bioavailability of insulin detemir is approximately 60%.

Distribution and Elimination

More than 98% insulin detemir in the bloodstream is bound to albumin. LEVEMIR has a small apparent volume of distribution of approximately 0.1 L/kg. LEVEMIR, after subcutaneous administration, has a terminal half-life of 5 to 7 hours depending on dose.

Special Populations

Children and Adolescents- The pharmacokinetic properties of LEVEMIR were investigated in children (6 to 12 years) and adolescents (13 to 17 years) and adults with type 1 diabetes. Similar to NPH human insulin, slightly higher plasma Area Under the Curve (AUC) and C_{max} were observed in children by 10% and 24%, respectively, compared to adolescents and adults. There was no difference in pharmacokinetics between adolescents and adults.

Geriatrics- In a clinical trial investigating differences in pharmacokinetics of a single subcutaneous dose of LEVEMIR in young (25 to 35 years) versus elderly (≥ 68 years) healthy subjects, higher insulin AUC levels (up to 35%) were found in elderly subjects due to a reduced clearance. As with other insulin preparations, LEVEMIR should always be titrated according to individual requirements.

Gender- In controlled clinical trials, no clinically relevant difference between genders is seen in pharmacokinetic parameters based on subgroup analyses.

Race- In two trials in healthy Japanese and Caucasian subjects, there were no clinically relevant differences seen in pharmacokinetic parameters. Pharmacokinetics and pharmacodynamics of LEVEMIR were investigated in a clamp trial comparing patients with type 2 diabetes of Caucasian, African-American, and Latino origin. Dose-response relationships were comparable for LEVEMIR in these three populations.

Renal impairment- Individuals with renal impairment showed no difference in pharmacokinetic parameters as compared to healthy volunteers. However, literature reports have shown that clearance of human insulin is decreased in renally impaired patients. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR, may be necessary in patients with renal dysfunction (see Precautions, Renal

Impairment).

Hepatic impairment- Individuals with severe hepatic dysfunction, without diabetes, were observed to have lower AUCs as compared to healthy volunteers. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR, may be necessary in patients with hepatic dysfunction (see Precautions, Hepatic Impairment).

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

Smoking- The effect of smoking on the pharmacokinetics and pharmacodynamics of LEVEMIR has not been studied.

Clinical Studies

The efficacy and safety of LEVEMIR given once-daily at bedtime or twice-daily (before breakfast and at bedtime, before breakfast and with the evening meal, or at 12-hour intervals) was compared to that of once-daily or twice-daily NPH human insulin or once-daily insulin glargine in non-blinded, randomized, parallel studies of 6004 patients with diabetes (3724 with type 1, and 2280 with type 2). In general, patients treated with LEVEMIR achieved levels of glycemic control similar to those treated with NPH human insulin or insulin glargine, as measured by glycosylated hemoglobin (HbA_{1c}).

Type 1 Diabetes – Adult

In one non-blinded clinical study (Study A, n=409), adult patients with type 1 diabetes were randomized to treatment with either LEVEMIR at 12-hour intervals, LEVEMIR morning and bedtime or NPH human insulin morning and bedtime. Insulin aspart was also administered before each meal. At 16 weeks of treatment, the combined LEVEMIR-treated patients had similar HbA_{1c} and fasting plasma glucose (FPG) reductions to NPH-treated patients (Table 1). Differences in timing of LEVEMIR administration (or flexible dosing) had no effect on HbA_{1c}, FPG, body weight, or risk of having hypoglycemic episodes.

Overall glycemic control achieved with LEVEMIR was compared to that achieved with insulin glargine in a randomized, non-blinded, clinical study (Study B, n=320) in which patients with type 1 diabetes were treated for 26 weeks with either twice-daily (morning and bedtime) LEVEMIR or once-daily (bedtime) insulin glargine. Insulin aspart was administered before each meal. LEVEMIR-treated patients had a decrease in HbA_{1c} similar to that of insulin glargine-treated patients.

In a randomized, controlled clinical study (Study C, n=749), patients with type 1 diabetes were treated with once-daily (bedtime) LEVEMIR or NPH human insulin, both in combination with human soluble insulin before each meal for 6 months. LEVEMIR and NPH human insulin had a similar effect on HbA_{1c}.

Table 1: Efficacy and Insulin Dosage in Type 1 Diabetes Mellitus - Adult

<u>Study A</u>	
Treatment duration	16 weeks
Treatment in combination with	NovoLog [®] (insulin aspart)

<u>LEVEMIR NPH</u>			
Number of subjects treated	276	133	
HbA_{1c} (%)			
Baseline	8.64	8.51	
End of study adjusted mean	7.76	7.94	
Mean change from baseline	-0.82	-0.60	
Fasting Plasma Glucose (mg/dL)			
End of study adjusted mean	168	202	
Mean change from baseline	-42.48	-10.80	
Daily Basal Insulin Dose (U/kg)			
Prestudy mean	0.36	0.39	
End of study mean	0.49	0.45	
Daily Bolus Insulin Dose (U/kg)			
Prestudy mean	0.40	0.40	
End of study mean	0.38	0.38	

Baseline values were included as covariates in an ANCOVA analysis.

Type 1 Diabetes – Pediatric

In a non-blinded, randomized, controlled clinical study (Study D, n=347), pediatric patients (age range 6 to 17) with type 1 diabetes were treated for 26 weeks with a basal-bolus insulin regimen. LEVEMIR and NPH human insulin were administered once- or twice-daily (bedtime or morning and bedtime) according to pretrial dose regimen. Bolus insulin aspart was administered before each meal. LEVEMIR-treated patients had a decrease in HbA_{1c} similar to that of NPH human insulin.

Table 2: Efficacy and Insulin Dosage in Type 1 Diabetes Mellitus - Pediatric
Study D

Treatment duration	26 weeks		
Treatment in combination with	NovoLog® (insulin aspart)		
<u>LEVEMIR NPH</u>			
Number of subjects treated	232	115	
HbA_{1c} (%)			
Baseline	8.75	8.77	
End of study adjusted mean	8.02	7.93	
Mean change from baseline	-0.72	-0.80	
Fasting Plasma Glucose (mg/dL)			
End of study adjusted mean	151.92	172.44	
Mean change from baseline	-45.00	-19.98	
Daily Basal Insulin Dose (U/kg)			
Prestudy mean	0.48	0.49	
End of study mean	0.67	0.64	
Daily Bolus Insulin Dose (U/kg)			
Prestudy mean	0.52	0.47	
End of study mean	0.52	0.51	

Type 2 Diabetes – Adult

In a 24-week, non-blinded, randomized, clinical study (Study E, n=476), LEVEMIR administered twice-daily (before breakfast and evening) was compared to a similar regimen of NPH human insulin as part of a regimen of combination therapy with one or

two of the following oral antidiabetes agents (metformin, insulin secretagogue, or α -glucosidase inhibitor). LEVEMIR and NPH similarly lowered HbA_{1c} from baseline (Table 3).

Table 3: Efficacy and Insulin Dosage in Type 2 Diabetes Mellitus

<u>Study E</u>			
Treatment duration	24 weeks		
Treatment in combination with	OAD		
<u>LEVEMIR NPH</u>			
Number of subjects treated	237	239	
HbA_{1c} (%)			
Baseline	8.61	8.51	
End of study adjusted mean	6.58	6.46	
Mean change from baseline	-1.84	-1.90	
Proportion achieving HbA _{1c} ≤ 7%	70%	74%	
Fasting Plasma Glucose (mg/dL)			
End of study adjusted mean	119.16	113.40	
Mean change from baseline	-75.96	-74.34	
Daily Insulin Dose (U/kg)			
End of study mean	0.77	0.52	

In a 22-week, non-blinded, randomized, clinical study (Study F, n=395) in adults with Type 2 diabetes, LEVEMIR and NPH human insulin were given once- or twice-daily as part of a basal-bolus regimen. As measured by HbA_{1c} or FPG, LEVEMIR had efficacy similar to NPH human insulin.

INDICATIONS AND USAGE

LEVEMIR is indicated for once- or twice-daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long acting) insulin for the control of hyperglycemia.

CONTRAINDICATIONS

LEVEMIR is contraindicated in patients hypersensitive to insulin detemir or one of its excipients.

WARNINGS

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

Glucose monitoring is recommended for all patients with diabetes.

LEVEMIR is not to be used in insulin infusion pumps.

Any change of insulin dose should be made cautiously and only under medical supervision. Changes in insulin strength, timing of dosing, manufacturer, type

(e.g., regular, NPH, or insulin analogs), species (animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

Concomitant oral antidiabetic treatment may need to be adjusted.

Needles and Levemir FlexPen must not be shared.

PRECAUTIONS

General

Inadequate dosing or discontinuation of treatment may lead to hyperglycemia and, in patients with type 1 diabetes, diabetic ketoacidosis. The first symptoms of hyperglycemia usually occur gradually over a period of hours or days. They include nausea, vomiting, drowsiness, flushed dry skin, dry mouth, increased urination, thirst and loss of appetite as well as acetone breath. Untreated hyperglycemic events are potentially fatal.

LEVEMIR is not intended for intravenous or intramuscular administration. The prolonged duration of activity of insulin detemir is dependent on injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia. Absorption after intramuscular administration is both faster and more extensive than absorption after subcutaneous administration.

LEVEMIR should not be diluted or mixed with any other insulin preparations (see PRECAUTIONS, Mixing of Insulins).

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

Lipodystrophy and hypersensitivity are among potential clinical adverse effects associated with the use of all insulins.

As with all insulin preparations, the time course of LEVEMIR action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan.

Hypoglycemia

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of LEVEMIR. Hypoglycemia is the most common adverse effect of insulins. 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.

The time of occurrence of hypoglycemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen or timing of dosing is changed. In patients being switched from other intermediate or long-acting insulin preparations to once- or twice-daily LEVEMIR, dosages can be prescribed on a unit-to-unit basis; however, as with all insulin preparations, dose and timing of administration may need to be adjusted to reduce the risk of hypoglycemia (see DOSAGE AND ADMINISTRATION, Changeover to LEVEMIR).

Renal Impairment

As with other insulins, the requirements for LEVEMIR may need to be adjusted in patients with renal impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Hepatic Impairment

As with other insulins, the requirements for LEVEMIR may need to be adjusted in patients with hepatic impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Injection Site and Allergic Reactions

As with any insulin therapy, lipodystrophy may occur at the injection site and delay insulin absorption. Other injection site reactions with insulin therapy may include redness, pain, itching, hives, swelling, and inflammation. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of LEVEMIR.

In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic allergy: Generalized allergy to insulin, which is less common but potentially more serious, may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life-threatening.

Intercurrent Conditions

Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances, or other stresses.

Information for Patients

LEVEMIR must only be used if the solution appears clear and colorless with no visible particles (see DOSAGE AND ADMINISTRATION, Preparation and Handling). Patients should be informed about potential risks and advantages of LEVEMIR therapy, including the possible side effects. Patients should be offered continued education and advice on insulin therapies, injection technique, life-style management, regular glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and

hyperglycemia, adherence to meal planning, complications of insulin therapy, timing of dosage, instruction for use of injection devices and proper storage of insulin. Patients should be informed that frequent, patient-performed blood glucose measurements are needed to achieve effective glycemic control to avoid both hyperglycemia and hypoglycemia. Patients must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, or skipped meals. Refer patients to the LEVEMIR "Patient Information" circular for additional information.

As with all patients who have diabetes, the ability to concentrate and/or react may be impaired as a result of hypoglycemia or hyperglycemia.

Patients with diabetes should be advised to inform their health care professional if they are pregnant or are contemplating pregnancy (see PRECAUTIONS, Pregnancy).

Laboratory Tests

As with all insulin therapy, the therapeutic response to LEVEMIR should be monitored by periodic blood glucose tests. Periodic measurement of HbA_{1c} is recommended for the monitoring of long-term glycemic control.

Drug Interactions

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

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

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

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia. In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent.

The results of *in-vitro* and *in-vivo* protein binding studies demonstrate that there is no clinically relevant interaction between insulin detemir and fatty acids or other protein bound drugs.

Mixing of Insulins

If LEVEMIR is mixed with other insulin preparations, the profile of action of one or both

individual components may change. Mixing LEVEMIR with insulin aspart, a rapid acting insulin analog, resulted in about 40% reduction in $AUC_{(0-2h)}$ and C_{max} for insulin aspart compared to separate injections when the ratio of insulin aspart to LEVEMIR was less than 50%.

LEVEMIR should not be mixed or diluted with any other insulin preparations.

Carcinogenicity, Mutagenicity, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed. Insulin detemir tested negative for genotoxic potential in the *in-vitro* reverse mutation study in bacteria, human peripheral blood lymphocyte chromosome aberration test, and the *in-vivo* mouse micronucleus test.

Pregnancy: Teratogenic Effects: Pregnancy Category C

In a fertility and embryonic development study, insulin detemir was administered to female rats before mating, during mating, and throughout pregnancy at doses up to 300 nmol/kg/day (3 times the recommended human dose, based on plasma Area Under the Curve (AUC) ratio). Doses of 150 and 300 nmol/kg/day produced numbers of litters with visceral anomalies. Doses up to 900 nmol/kg/day (approximately 135 times the recommended human dose based on AUC ratio) were given to rabbits during organogenesis. Drug-dose related increases in the incidence of fetuses with gall bladder abnormalities such as small, bilobed, bifurcated and missing gall bladders were observed at a dose of 900 nmol/kg/day. The rat and rabbit embryofetal development studies that included concurrent human insulin control groups indicated that insulin detemir and human insulin had similar effects regarding embryotoxicity and teratogenicity.

Nursing mothers

It is unknown whether LEVEMIR is excreted in significant amounts in human milk. For this reason, caution should be exercised when LEVEMIR is administered to a nursing mother. Patients with diabetes who are lactating may require adjustments in insulin dose, meal plan, or both.

Pediatric use

In a controlled clinical study, HbA_{1c} concentrations and rates of hypoglycemia were similar among patients treated with LEVEMIR and patients treated with NPH human insulin.

Geriatric use

Of the total number of subjects in intermediate and long-term clinical studies of LEVEMIR, 85 (type 1 studies) and 363 (type 2 studies) were 65 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic

reactions. Hypoglycemia may be difficult to recognize in the elderly.

ADVERSE REACTIONS

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

Body as Whole: allergic reactions (see Precautions, Allergy).

Skin and Appendages: lipodystrophy, pruritus, rash. Mild injection site reactions occurred more frequently with LEVEMIR than with NPH human insulin and usually resolved in a few days to a few weeks (see Precautions, Allergy).

Other:

Hypoglycemia: (see Warnings and Precautions).

In trials of up to 6 months duration in patients with type 1 and type 2 diabetes, the incidence of severe hypoglycemia with LEVEMIR was comparable to the incidence with NPH, and, as expected, greater overall in patients with type 1 diabetes (Table 4).

Weight gain:

In trials of up to 6 months duration in patients with type 1 and type 2 diabetes, LEVEMIR was associated with somewhat less weight gain than NPH (Table 4). Whether these observed differences represent true differences in the effects of LEVEMIR and NPH insulin is not known, since these trials were not blinded and the protocols (e.g., diet and exercise instructions and monitoring) were not specifically directed at exploring hypotheses related to weight effects of the treatments compared. The clinical significance of the observed differences has not been established.

Table 4: Safety Information on Clinical Studies*

Treatment	# of subjects	<u>Weight (kg)</u>		<u>Hypoglycemia</u> (events/subject/month)		Major**
		Baseline	End of treatment	Baseline	End of treatment	
Minor***						
Type 1						
<u>Study A</u> LEVEMIR	N=276	75.0	75.1	0.045	2.184	
NPH	N=133	75.7	76.4	0.035	3.063	
<u>Study C</u> LEVEMIR	N=492	76.5	76.3	0.029	2.397	
NPH	N=257	76.1	76.5	0.027	2.564	
<u>Study D</u> Pediatric	LEVEMIR N=232	N/A	N/A	0.076	2.677	
NPH	N=115	N/A	N/A	0.083	3.203	
Type 2						
<u>Study E</u> LEVEMIR	N=237	82.7	83.7	0.001	0.306	
NPH	N=239	82.4	85.2	0.006	0.595	
<u>Study F</u> LEVEMIR	N=195	81.8	82.3	0.003	0.193	
NPH	N=200	79.6	80.9	0.006	0.235	

* See CLINICAL STUDIES section for description of individual studies

** Major = requires assistance of another individual because of neurologic impairment

*** Minor = plasma glucose <56 mg/dl, subject able to deal with the episode him/herself

OVERDOSAGE

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. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid reoccurrence of hypoglycemia.

DOSAGE AND ADMINISTRATION

LEVEMIR can be administered once- or twice-daily. The dose of LEVEMIR should be adjusted according to blood glucose measurements. The dosage of LEVEMIR should be individualized based on the physician's advice, in accordance with the needs of the patient.

- For patients treated with LEVEMIR once-daily, the dose should be administered with the evening meal or at bedtime.
- For patients who require twice-daily dosing for effective blood glucose control, the evening dose can be administered either with the evening meal, at bedtime, or 12 hours after the morning dose.

LEVEMIR should be administered by subcutaneous injection in the thigh, abdominal wall, or upper arm. Injection 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.

Dose Determination for LEVEMIR

- For patients with type 1 or type 2 diabetes on basal-bolus treatment, changing the basal insulin to LEVEMIR can be done on a unit-to-unit basis. The dose of LEVEMIR should then be adjusted to achieve glycemic targets. In some patients with type 2 diabetes, more LEVEMIR may be required than NPH insulin. In a clinical study, the mean dose at end of treatment was 0.77 U/kg for LEVEMIR and 0.52 IU/kg for NPH human insulin (see Table 3).
- For patients currently receiving only basal insulin, changing the basal insulin to LEVEMIR can be done on a unit-to-unit basis.

- For insulin-naïve patients with type 2 diabetes who are inadequately controlled on oral antidiabetic drugs, LEVEMIR should be started at a dose of 0.1 to 0.2 U/kg once-daily in the evening or 10 units once- or twice-daily, and the dose adjusted to achieve glycemic targets.
- As with all insulins, close glucose monitoring is recommended during the transition and in the initial weeks thereafter. Dose and timing of concurrent short-acting insulins or other concomitant antidiabetic treatment may need to be adjusted.

Preparation and Handling

LEVEMIR should be inspected visually prior to administration and should only be used if the solution appears clear and colorless.

LEVEMIR should not be mixed or diluted with any other insulin preparations.

After each injection, patients must **remove the needle without recapping** and dispose of it in a puncture-resistant container. Used syringes, needles, or lancets should be placed in “sharps” containers (such as red biohazard containers), hard plastic containers (such as detergent bottles), or metal containers (such as an empty coffee can). Such containers should be sealed and disposed of properly.

HOW SUPPLIED

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

10 mL vial NDC 0169-3687-12

3 mL PenFill® cartridges* NDC 0169-3305-11

3 mL InnoLet® NDC 0169-2312-11

3 mL FlexPen® NDC 0169-6439-10

*LEVEMIR PenFill® cartridges are for use with Novo Nordisk 3 mL PenFill® cartridge compatible insulin delivery devices and NovoFine® disposable needles.

RECOMMENDED STORAGE

Unused LEVEMIR should be stored between 2° and 8°C (36° to 46°F). *Do not freeze. Do not use LEVEMIR if it has been frozen.*

Vials:

After initial use, vials should be stored in a refrigerator, never in a freezer. If refrigeration is not possible, the in-use vial can be kept unrefrigerated at room temperature, below 30°C (86°F), for up to 42 days, as long as it is kept as cool as possible and away from direct heat and light.

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, FlexPen[®] or InnoLet[®]:

After initial use, a cartridge (PenFill[®]) or a prefilled syringe (including FlexPen[®] or InnoLet[®]) may be used for up to 42 days if it is kept at room temperature, below 30°C (86°F). In-use cartridges and prefilled syringes in-use must NOT be stored in a refrigerator and must NOT be stored with the needle in place. Keep all cartridges and prefilled syringes away from direct heat and sunlight.

Not in-use (unopened) LEVEMIR PenFill[®], FlexPen[®] or InnoLet[®] can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused cartridges and prefilled syringes in the carton so they will stay clean and protected from light.

The storage conditions are summarized in the following table:

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 42 days Until expiration date 42 days
refrigerated/room temperature
3 mL PenFill[®]

cartridges 42 days Until expiration date 42 days **(Do not refrigerate)**
3 mL InnoLet[®] 42 days Until expiration date 42 days **(Do not refrigerate)**
3 mL FlexPen[®] 42 days Until expiration date 42 days **(Do not refrigerate)**

Rx Only

Date of Issue: July 15, 2009

Version: 5

Novo Nordisk[®], Levemir[®], NovoLog[®], FlexPen[®], InnoLet[®], PenFill[®] and NovoFine[®] are

registered trademarks owned by Novo Nordisk A/S.

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Levemir® is covered by US Patent Nos. 5,750,497; 5,866,538; 6,011,007; 6,869,930 and other patents pending.

FlexPen® is covered by US Patent Nos. 6,004,297; 6,235,004; 6,582,404 and other patents pending.

Manufactured for:
Novo Nordisk Inc.
Princeton, NJ 08540
www.novonordisk-us.com

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

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**

.....RECENT MAJOR CHANGES.....

- Dosage and Administration (2.3) 7/2009
- 1 Warnings and Precautions, Administration (5.1) 10/2009

.....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 at least every 6 days, change the infusion set, and the infusion set insertion site at least every 3 days. 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® (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 (5.6).

.....**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](tel: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).

-----**USE IN SPECIFIC POPULATIONS**-----

- Pediatric: Has not been studied in children with type 2 diabetes. Has not been studied in children with type 1 diabetes <2 years of age (8.4).

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

Revised: 6/2011

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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 (5.8, 5.9), 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 at least every 6 days, change the infusion sets and the infusion set insertion site at least every 3 days.**

The following insulin pumps[†] have been used in NovoLog clinical or *in vitro* studies conducted by Novo Nordisk, the manufacturer of NovoLog:

- Medtronic Paradigm[®] 512 and 712
- MiniMed 508
- Disetronic[®] D-TRON[®] and H-TRON[®]

Before using a different insulin pump with NovoLog, read the pump label to make sure the pump has been evaluated with NovoLog.

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), 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 3 mL PenFill cartridge delivery device

(with or without the addition of a NovoPen® 3 PenMate®)
with NovoFine® disposable needles
- 3 mL NovoLog FlexPen

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.

Needles and NovoLog FlexPen must not be shared.

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 Continuous Subcutaneous 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 (5.8, 5.9)*, *How Supplied/Storage and Handling (16.2)*, and *Patient Counseling Information (17.2)*].

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 (5.8, 5.9)*, *How Supplied/Storage and Handling (16.2)*, and *Patient Counseling Information (17.2)*].

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 \geq 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 \geq 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. NovoLog has not been studied in pediatric patients younger than 2 years of age. NovoLog has not been studied in pediatric patients with type 2 diabetes. 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 $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8.

<< OLE Object: Picture (Metafile) >>

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, sodium chloride 0.58 mg/mL and water for injection. 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)].

<< OLE Object: Picture (Metafile) >>

Figure 2. Serial mean serum glucose collected up to 6 hours following a single premeal 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).

<< OLE Object: Picture (Metafile) >>

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.

<< OLE Object: Picture (Metafile) >>

Figure 4. Serial mean serum free insulin concentration collected up to 6 hours following a single premeal 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=107) 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 nonobese 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 ≥ 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/m²). The pharmacokinetic parameters, AUC and C_{max}, of NovoLog were generally unaffected by BMI in the different groups - BMI 19-23 kg/m² (N=4); BMI 23-27 kg/m² (N=7); BMI 27-32 kg/m² (N=6) and BMI >32 kg/m² (N=6). Clearance of NovoLog was reduced by 28% in patients with BMI >32 kg/m² compared to patients with BMI <23 kg/m².

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 sixmonth, openlabel, 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)*		
Weight Change from baseline (kg)*	75.3 ± 14.5	75.9 ± 13.1
	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)*		
Weight Change from baseline (kg)*	50.6 ± 19.6	

2.7 ± 3.5 48.7 ± 15.8

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_{1c} 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)*		
Weight Change from baseline (kg)*	88.4 ± 13.3	

1.2 ± 3.0 85.8 ± 14.8

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)*		
Weight Change from baseline (kg)*	77.4 ± 16.1	

	0.1 ± 3.5	74.8 ± 13.8
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-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)*		
Weight Change from baseline (kg)*	54.1 ± 19.7	

	1.8 ± 2.1	55.5 ± 19.0
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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)*		
Weight Change from baseline (kg)*	96.4 ± 17.0	
	1.7 ± 3.7	96.9 ± 17.9
	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	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:

Once a cartridge or a NovoLog FlexPen 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. A NovoLog FlexPen or cartridge in use must NOT be stored in the refrigerator. Keep the NovoLog FlexPen and all PenFill cartridges away from direct heat and sunlight. Unpunctured NovoLog FlexPen and PenFill cartridges can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused NovoLog FlexPen and PenFill cartridges 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 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 6 days of use or after exposure to temperatures that exceed 37°C (98.6°F). The infusion set and the infusion set insertion site should be changed at least every 3 days.

Summary of Storage Conditions:

The storage conditions are summarized in the following table:

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

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	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, lifestyle 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.

The following insulin pumps[†] have been used in NovoLog clinical or *in vitro* studies conducted by Novo Nordisk, the manufacturer of NovoLog:

- Medtronic Paradigm[®] 512 and 712
- MiniMed 508
- Disetronic[®] D-TRON[®] and H-TRON[®]

Before using another insulin pump with NovoLog, read the pump label to make sure the pump has been evaluated with NovoLog.

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), insulin in the reservoir should be replaced at least every 6 days; infusion sets and infusion set insertion sites should be changed at least every 3 days.

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 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

See separate leaflet.

Rx only

Date of Issue: June 2011

Version: 19

Novo Nordisk[®], NovoLog[®], NovoPen[®] 3, PenFill[®], Novolin[®], FlexPen[®], PenMate[®] and NovoFine[®] are registered trademarks of Novo Nordisk A/S.

NovoLog[®] is covered by US Patent Nos. 5,618,913, 5,866,538, and other patents pending.

FlexPen[®] is covered by US Patent Nos. 6,582,404, 6,004,297, 6,235,004, and other patents pending.

PenFill[®] is covered by US Patent No. 5,693,027.

†The brands listed are the registered trademarks of their respective owners and are not trademarks of Novo Nordisk A/S.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NovoLog Mix 70/30 safely and effectively. See full prescribing information for NovoLog Mix 70/30.

**NovoLog® Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin])
Suspension for subcutaneous injection
Initial U.S. Approval: 2001**

-----RECENT MAJOR CHANGES-----

- Indications and Usage (1) 5/2010
- Dosage and Administration (2.1) 5/2010

-----INDICATIONS AND USAGE-----

NovoLog Mix 70/30 is an insulin analog indicated to improve glycemic control in patients with diabetes mellitus.

Important Limitations of Use: In premix insulins, such as NovoLog Mix 70/30, the proportions of rapid acting and long acting insulins are fixed and do not allow for basal versus prandial dose adjustments (1).

-----DOSAGE AND ADMINISTRATION-----

- Only for subcutaneous injection (2.1).
Type 1 DM: dose within 15 minutes before meal initiation.
Type 2 DM: dose within 15 minutes before or after starting a meal.
- Do not administer intravenously (2.1).
- Do not use in insulin infusion pumps (2.1).
- Must be resuspended immediately before use (2.2).

-----DOSAGE FORMS AND STRENGTHS-----

Each presentation contains 100 Units of insulin aspart per mL (U-100) (3)

- 10 mL vials
- 3 mL NovoLog Mix 70/30 FlexPen

-----CONTRAINDICATIONS-----

- Do not use during episodes of hypoglycemia (4).
- Do not use in patients with hypersensitivity to NovoLog Mix 70/30 or one of its excipients (4).

-----WARNINGS AND PRECAUTIONS-----

- NovoLog Mix 70/30 should not be mixed with any other insulin product (5.1).
- 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 in settings of poor glycemic control, can cause hypokalemia. Use caution in patients predisposed to hypokalemia (5.3).
- Like all insulins, NovoLog Mix 70/30 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 Mix 70/30 (5.6).

-----**ADVERSE REACTIONS**-----

Adverse reactions observed with insulin therapy 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](tel:1-800-727-6500) or FDA at [1-800-FDA-1088](tel: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 (MAO) inhibitors, propoxyphene, salicylates, somatostatin analog (e.g. octreotide), 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 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.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NovoLog Mix 70/30 is an insulin analog indicated to improve glycemic control in patients with diabetes mellitus.

Important Limitations of Use:

In premix insulins, such as NovoLog Mix 70/30, the proportions of rapid acting and long acting insulins are fixed and do not allow for basal versus prandial dose adjustments.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

NovoLog Mix 70/30 is an insulin analog with an earlier onset and intermediate duration of action in comparison to the basal human insulin premix. The addition of protamine to the rapid-acting aspart insulin analog (NovoLog) results in insulin activity that is 30% short-acting and 70% long-acting. NovoLog Mix 70/30 is typically dosed on a twice-daily basis (with each dose intended to cover 2 meals or a meal and a snack). The dosage of NovoLog Mix 70/30 must be individualized. The written prescription for NovoLog Mix 70/30 should include the full name, to avoid confusion with NovoLog (insulin aspart) and Novolin 70/30 (human premix).

NovoLog Mix 70/30 should appear uniformly white and cloudy. Do not use it if it looks clear or if it contains solid particles. NovoLog Mix 70/30 should not be used after the printed expiration date.

NovoLog Mix 70/30 should be administered by subcutaneous injection in the abdominal region, buttocks, thigh, or upper arm. NovoLog Mix 70/30 has a faster onset of action than human insulin premix 70/30 and should be dosed within 15 minutes before meal initiation for patients with type 1 diabetes. For patients with type 2 diabetes, dosing should occur within 15 minutes before or after meal initiation. Injection sites should be rotated within the same region to reduce the risk of lipodystrophy. As with all insulins, the duration of action may vary according to the dose, injection site, blood flow, temperature, and level of physical activity.

NovoLog Mix 70/30 should not be administered intravenously or used in insulin infusion pumps. Dose regimens of NovoLog Mix 70/30 will vary among patients and should be determined by the health care professional familiar with the patient's recommended glucose treatment goals, metabolic needs, eating habits, and other lifestyle variables.

2.2 Resuspension

NovoLog Mix 70/30 is a suspension that must be visually inspected and resuspended

immediately before use.

The NovoLog Mix 70/30 vial should be rolled gently in your hands in a horizontal position 10 times to mix it. The rolling procedure must be repeated until the suspension appears uniformly white and cloudy. Inject immediately. Resuspension is easier when the insulin has reached room temperature.

The NovoLog Mix 70/30 FlexPen should be rolled 10 times gently between your hands in a horizontal position. Thereafter, turn the NovoLog Mix 70/30 FlexPen upside down so that the glass ball moves from one end of the reservoir to the other. Do this at least 10 times. The rolling and turning procedure must be repeated until the suspension appears uniformly white and cloudy. Inject immediately. Before each subsequent injection, turn the disposable NovoLog Mix 70/30 FlexPen upside down so that the glass ball moves from one end of the reservoir to the other at least 10 times and until the suspension appears uniformly white and cloudy. Inject immediately.

3 DOSAGE FORMS AND STRENGTHS

NovoLog Mix 70/30 is available in the following package sizes: each presentation contains 100 units of insulin aspart per mL (U-100).

- 10 mL vials
- 3 mL NovoLog Mix 70/30 FlexPen

4 CONTRAINDICATIONS

NovoLog Mix 70/30 is contraindicated

- during episodes of hypoglycemia
- in patients with hypersensitivity to NovoLog Mix 70/30 or one of its excipients.

5 WARNINGS AND PRECAUTIONS

5.1 Administration

The short and long-acting components of insulin mixes, including NovoLog Mix 70/30, cannot be titrated independently. Because NovoLog Mix 70/30 has peak pharmacodynamic activity between 1-4 hours after injection, it should be administered within 15 minutes of meal initiation [see *Clinical Pharmacology (12)*]. The dose of insulin required to provide adequate glycemic control for one of the meals may result in hyper- or hypoglycemia for the other meal. The pharmacodynamic profile may also be inadequate for patients who require more frequent meals.

NovoLog Mix 70/30 should not be mixed with any other insulin product.

NovoLog Mix 70/30 should not be used intravenously.

NovoLog Mix 70/30 should not be used in insulin infusion pumps.

Glucose monitoring is recommended for all patients with diabetes. 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. Changes may also be necessary during illness, emotional stress, and other physiologic stress in addition to changes in meals and exercise.

The pharmacokinetic and pharmacodynamic profiles of all insulins may be altered by the

site used for injection and the degree of vascularization of the site. Smoking, temperature, and exercise contribute to variations in blood flow and insulin absorption. These and other factors contribute to inter- and intra-patient variability.

Needles and NovoLog Mix 70/30 FlexPen must not be shared.

5.2 Hypoglycemia

Hypoglycemia is the most common adverse effect of insulin therapy, including NovoLog Mix 70/30. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even 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 Mix 70/30.

The timing of hypoglycemia may reflect the time-action profile of the insulin formulation [see *Clinical Pharmacology* (12)]. Other factors, such as changes in dietary 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 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 long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control [see *Drug Interactions* (7)].

5.3 Hypokalemia

All insulin products, including NovoLog Mix 70/30, 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 or patients taking medications sensitive to potassium concentrations).

5.4 Renal Impairment

Clinical or pharmacology studies with NovoLog Mix 70/30 in diabetic patients with various degrees of renal impairment have not been conducted. As with other insulins, the requirements for NovoLog Mix 70/30 may be reduced in patients with renal impairment [see *Clinical Pharmacology* (12.3)].

5.5 Hepatic Impairment

Clinical or pharmacology studies with NovoLog Mix 70/30 in diabetic patients with various degrees of hepatic impairment have not been conducted. As with other insulins, the requirements for NovoLog Mix 70/30 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 reactions such as erythema, edema or pruritus at the site of NovoLog Mix 70/30 injection. These reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of NovoLog Mix 70/30. In some instances, these reactions may be related to the insulin molecule, other components in the insulin preparation including protamine and cresol, components in skin cleansing agents, or injection techniques. Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient.

Systemic Reactions- 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.

5.7 Antibody Production

Specific anti-insulin antibodies as well as cross-reacting anti-insulin antibodies were monitored in a 3-month, open-label comparator trial as well as in a long-term extension trial. Changes in cross-reactive antibodies were more common after NovoLog Mix 70/30 than with Novolin 70/30 but these changes did not correlate with change in HbA_{1c} or increase in insulin dose. The clinical significance of these antibodies has not been established. Antibodies did not increase further after long-term exposure (>6 months) to NovoLog Mix 70/30.

6 ADVERSE REACTIONS

Clinical Trial Experience

Clinical trials are conducted under widely varying designs, therefore, 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 Mix 70/30 [see *Warnings and Precautions (5.2)*]. NovoLog Mix 70/30 should not be used during episodes of hypoglycemia [see *Contraindications (4) and Warnings and Precautions (5)*].

- *Insulin initiation and glucose control intensification*

Intensification or rapid improvement in glucose control has been associated with 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 Mix 70/30, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection sites within the same region to reduce the risk of lipodystrophy.

- Weight gain

Weight gain can occur with some insulin therapies, including NovoLog Mix 70/30, and has been attributed to the anabolic effects of insulin and the decrease in glycosuria.

- 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 a clinical trial with NovoLog Mix 70/30 in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below. The trial was a three-month, open-label trial in patients with Type 1 or Type 2 diabetes who were treated twice daily (before breakfast and before supper) with NovoLog Mix 70/30.

**Table 1: Treatment-Emergent Adverse Events in Patients with Type 1 diabetes mellitus
(Adverse events with frequency \geq 5% are included.)**

NovoLog Mix 70/30

(N=55) Novolin 70/30

Preferred Term	(N=49)					
	N	%	N	%		
Hypoglycemia	38	69	37	76		
Headache	19	35	6	12		
Influenza-like symptoms	7		13	1	2	
Dyspepsia	5	9	3	6		
Back pain	4	7	2	4		
Diarrhea	4	7	3	6		
Pharyngitis	4	7	1	2		
Rhinitis	3	5	6	12		
Skeletal pain	3	5	2	4		
Upper respiratory tract infection			3	5	1	2

**Table 2: Treatment-Emergent Adverse Events in Patients with Type 2 diabetes mellitus
(Adverse events with frequency \geq 5% are included.)**

NovoLog Mix 70/30

(N=85) Novolin 70/30

Preferred Term	(N=102)					
	N	%	N	%		
Hypoglycemia	40	47	51	50		
Upper respiratory tract infection			10	12	6	6
Headache	8	9	8	8		
Diarrhea	7	8	2	2		
Neuropathy	7	8	2	2		
Pharyngitis	5	6	4	4		
Abdominal pain	4	5	0	0		
Rhinitis	4	5	2	2		

Postmarketing Data

Additional adverse reactions have been identified during post-approval use of NovoLog Mix 70/30. Because these adverse reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency. They include medication errors in which other insulins have been accidentally substituted for NovoLog Mix 70/30 [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 such patients.

An open-label, randomized study compared the safety and efficacy of NovoLog (the rapid-acting component of NovoLog Mix 70/30) versus human insulin in the treatment of pregnant women with Type 1 diabetes (322 exposed pregnancies (NovoLog: 157, human insulin: 165)). Two-thirds of the enrolled patients were already pregnant when they entered the study. Since only one-third of the patients enrolled before conception, the study was not large enough to evaluate the risk of congenital malformations. Mean HbA_{1c} of ~ 6% was observed in both groups during pregnancy, and there was no significant difference in the incidence of maternal hypoglycemia.

Animal reproduction studies have not been conducted with NovoLog Mix 70/30. However, subcutaneous reproduction and teratology studies have been performed with NovoLog (the rapid-acting component of NovoLog Mix 70/30) 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.

Female patients should be advised to discuss with their physician if they intend to, or if they become pregnant. There are no adequate and well-controlled studies of the use of NovoLog Mix 70/30 in pregnant women.

8.3 Nursing Mothers

It is unknown whether insulin aspart is excreted in human milk as occurs with human insulin. There are no adequate and well-controlled studies of the use of NovoLog Mix 70/30 or NovoLog in lactating women. Women with diabetes who are lactating may require adjustments of their insulin doses.

8.4 Pediatric Use

Safety and effectiveness of NovoLog Mix 70/30 have not been established in pediatric patients.

8.5 Geriatric Use

Clinical studies of NovoLog Mix 70/30 did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this population.

10 OVERDOSAGE

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.

11 DESCRIPTION

NovoLog Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin]) is a human insulin analog suspension containing 70% insulin aspart protamine crystals and 30% soluble insulin aspart. NovoLog Mix 70/30 is a blood-glucose-lowering agent with an earlier onset and an intermediate duration of action. Insulin aspart 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 (NovoLog) has the empirical formula $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8 Da.

<< OLE Object: Picture (Metafile) >>

Figure 1. Structural formula of insulin aspart

NovoLog Mix 70/30 is a uniform, white, sterile suspension that contains insulin aspart 100 Units/mL.

Inactive ingredients for the 10 mL vial are mannitol 36.4 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 19.6 mg/mL, disodium hydrogen phosphate dihydrate 1.25 mg/mL, sodium chloride 0.58 mg/mL, and protamine sulfate 0.32 mg/mL.

Inactive ingredients for the NovoLog Mix 70/30 FlexPen are glycerol 16.0 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 19.6 mg/mL, disodium hydrogen phosphate dihydrate 1.25 mg/mL, sodium chloride 0.877 mg/mL, and protamine sulfate 0.32 mg/mL. NovoLog Mix 70/30 has a pH of 7.20 - 7.44. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The primary activity of NovoLog Mix 70/30 is the regulation of glucose metabolism. Insulins, including NovoLog Mix 70/30, bind to the insulin receptors on muscle, liver 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

The two euglycemic clamp studies described below [see *Clinical Pharmacology (12.3)*] assessed glucose utilization after dosing of healthy volunteers. NovoLog Mix 70/30 has an earlier onset of action than human premix 70/30 in studies of normal volunteers and patients with diabetes. The onset of action is between 10-20 minutes for NovoLog Mix 70/30 compared to 30 minutes for Novolin 70/30. The mean \pm SD time to peak activity for NovoLog Mix 70/30 is 2.4 hr \pm 0.8 hr compared to 4.2 hr \pm 0.4 hr for Novolin 70/30. The duration of action may be as long as 24 hours (see Figure 2).

<< OLE Object: Microsoft Word Picture >>

Figure 2. Pharmacodynamic Activity Profile of NovoLog Mix 70/30 and Novolin 70/30 in healthy subjects.

12.3 Pharmacokinetics

The single substitution of the amino acid proline with aspartic acid at position B28 in insulin aspart (NovoLog) reduces the molecule's tendency to form hexamers as observed with regular human insulin. The rapid absorption characteristics of NovoLog are maintained by NovoLog Mix 70/30. The insulin aspart in the soluble component of NovoLog Mix 70/30 is absorbed more rapidly from the subcutaneous layer than regular human insulin. The remaining 70% is in crystalline form as insulin aspart protamine which has a prolonged absorption profile after subcutaneous injection.

Bioavailability and Absorption- The relative bioavailability of NovoLog Mix 70/30 compared to NovoLog and Novolin 70/30 indicates that the insulins are absorbed to similar extent. In euglycemic clamp studies in healthy volunteers (n=23) after dosing with NovoLog Mix 70/30 (0.2 U/kg), a mean maximum serum concentration (C_{max}) of 23.4 \pm 5.3 mU/L was reached after 60 minutes. The mean half-life ($t_{1/2}$) of NovoLog Mix 70/30 was about 8 to 9 hours. Serum insulin levels returned to baseline 15 to 18 hours after a subcutaneous dose of NovoLog Mix 70/30. Similar data were seen in a separate euglycemic clamp study in healthy volunteers (n=24) after dosing with NovoLog Mix 70/30 (0.3 U/kg). A C_{max} of 61.3 \pm 20.1 mU/L was reached after 85 minutes. Serum insulin levels returned to baseline 12 hours after a subcutaneous dose.

The C_{max} and the area under the insulin concentration-time curve (AUC) after administration of NovoLog Mix 70/30 was approximately 20% greater than those after administration of Novolin 70/30, (see Fig. 3 for pharmacokinetic profiles).

<< OLE Object: Microsoft Word Picture >>

Figure 3. Pharmacokinetic Profiles of NovoLog Mix 70/30 and Novolin 70/30

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

The effect of sex, age, obesity, ethnic origin, renal and hepatic impairment, pregnancy,

or smoking, on the pharmacodynamics and pharmacokinetics of NovoLog Mix 70/30 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 Mix 70/30. In 52-week studies, Sprague-Dawley rats were dosed subcutaneously with NovoLog, the rapid-acting component of NovoLog Mix 70/30, 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 found with NovoLog was not significantly different from that found with 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, NovoLog at subcutaneous doses up to 200 U/kg/day (approximately 32 times the human subcutaneous dose, based on U/body surface area) had no direct adverse effects on male and female fertility, or on general reproductive performance of animals.

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. However, the effect of NovoLog Mix 70/30 is more rapid in onset compared to Novolin (human insulin) 70/30 due to its faster absorption after subcutaneous injection.

14 CLINICAL STUDIES

14.1 NovoLog Mix 70/30 versus Novolin 70/30

In a three-month, open-label trial, patients with Type 1 (n=104) or Type 2 (n=187) diabetes were treated twice daily (before breakfast and before supper) with NovoLog Mix 70/30 or Novolin 70/30. Patients had received insulin for at least 24 months before the study. Oral hypoglycemic agents were not allowed within 1 month prior to the study or during the study. The small changes in HbA_{1c} were comparable across the treatment groups (see Table 3).

Table 3: Glycemic Parameters at the End of Treatment [Mean ± SD (N subjects)]

	NovoLog Mix 70/30	Novolin 70/30
	Type 1, N=104	
Fasting Blood Glucose (mg/dL)	174 ± 64 (48)	142 ± 59 (44)
1.5 Hour Post Breakfast (mg/dL)	187 ± 82 (48)	200 ± 82 (42)

1.5 Hour Post Dinner (mg/dL) 162 ± 77 (47) 171 ± 66 (41)
 HbA_{1c} (%) Baseline 8.4 ± 1.2 (51) 8.5 ± 1.1 (46)
 HbA_{1c} (%) Week 12 8.4 ± 1.1 (51) 8.3 ± 1.0 (47)

Type 2, N=187

Fasting Blood Glucose (mg/dL) 153 ± 40 (76) 152 ± 69 (93)
 1.5 Hour Post Breakfast (mg/dL) 182 ± 65 (75) 200 ± 80 (92)
 1.5 Hour Post Dinner (mg/dL) 168 ± 51 (75) 191 ± 65 (93)
 HbA_{1c} (%) Baseline 8.1 ± 1.2 (82) 8.2 ± 1.3 (98)
 HbA_{1c} (%) Week 12 7.9 ± 1.0 (81) 8.1 ± 1.1 (96)

The significance, with respect to the long-term clinical sequelae of diabetes, of the differences in postprandial hyperglycemia between treatment groups has not been established.

Specific anti-insulin antibodies as well as cross-reacting anti-insulin antibodies were monitored in the 3-month, open-label comparator trial as well as in a long-term extension trial.

14.2 Combination Therapy: Insulin and Oral Agents in Patients with Type 2 Diabetes

Trial 1:

In a 34-week, open-label trial, insulin-naïve patients with type 2 diabetes currently treated with 2 oral antidiabetic agents were switched to treatment with metformin and pioglitazone. During an 8-week optimization period metformin and pioglitazone were increased to 2500 mg per day and 30 or 45 mg per day, respectively. After the optimization period, subjects were randomized to receive either NovoLog Mix 70/30 twice daily added on to the metformin and pioglitazone regimen or continue the current optimized metformin and pioglitazone therapy. NovoLog Mix 70/30 was started at a dose of 6 IU twice daily (before breakfast and before supper). Insulin doses were titrated to a pre-meal glucose goal of 80-110 mg/dL. The total daily insulin dose at the end of the study was 56.9 ± 30.5 IU.

Table 4: Combination Therapy with Oral Agents and Insulin in Patients with Type 2 Diabetes Mellitus [Mean (SD)]

Treatment duration 24-weeks NovoLog Mix 70/30 + Metformin

+ Pioglitazone Metformin + Pioglitazone

	HbA _{1c}		
Baseline mean ± SD (n)	8.1 ± 1.0 (102)	8.1 ± 1.0 (98)	
End-of-study mean ± SD (n) - LOCF	6.6 ± 1.0 (93)	7.8 ± 1.2 (87)	
Adjusted Mean change from baseline ± SE (n)*	-1.6 ± 0.1 (93)	-0.3 ± 0.1 (87)	
	Treatment difference mean ± SE*		

95% CI* -1.3 ± 0.1

	(-1.6, -1.0)		
Percentage of subjects reaching HbA _{1c} <7.0%	76%	24%	
Percentage of subjects reaching HbA _{1c} ≤6.5%	59%	12%	
Fasting Blood Glucose (mg/dL)			

Baseline Mean ± SD (n)	173 ± 39.8 (93)	163 ± 35.4 (88)
End of Study Mean ± SD (n) – LOCF	130 ± 50.0 (90)	162 ± 40.8 (84)
Adjusted Mean change from baseline ± SE (n)*	-43.0 ± 5.3 (90)	-3.9 ± 5.3 (84)
End-of-Study Blood Glucose (Plasma) (mg/dL)		
2 Hour Post Breakfast	138 ± 42.8 (86)	188 ± 57.7 (74)
2 Hour Post Lunch	150 ± 41.5 (86)	176 ± 56.5 (74)
2 Hour Post Dinner	141 ± 57.8 (86)	195 ± 60.1 (74)
% of patients with severe hypoglycemia**	3	0
% of patients with minor hypoglycemia**	52	3
Weight gain at end of study (kg)**	4.6 ± 4.3 (92)	0.8 ± 3.2 (86)

*Adjusted mean per group, treatment difference, and 95% CI were obtained based on an ANCOVA model with treatment, FPG stratum, and secretagogue stratum as fixed factors and baseline HbA_{1c} as the covariate.

**If metabolic control is improved by intensified insulin therapy, an increased risk of hypoglycemia and weight gain may occur.

Trial 2:

In a 28-week, open-label trial, insulin-naïve patients with type 2 diabetes with fasting plasma glucose above 140 mg/dL currently treated with metformin ± thiazolidinedione therapy were randomized to receive either NovoLog Mix 70/30 twice daily [before breakfast and before supper] or insulin glargine once daily¹ (see Table 5). NovoLog Mix 70/30 was started at an average dose of 5-6 IU (0.07 ± 0.03 IU/kg) twice daily (before breakfast and before supper), and bedtime insulin glargine was started at 10-12 IU (0.13 ± 0.03 IU/kg). Insulin doses were titrated weekly by decrements or increments of -2 to +6 units per injection to a pre-meal glucose goal of 80-110 mg/dL. The metformin dose was adjusted to 2550 mg/day. Approximately one-third of the patients in each group were also treated with pioglitazone (30 mg/day). Insulin secretagogues were discontinued in order to reduce the risk of hypoglycemia. Most patients were Caucasian (53%), and the mean initial weight was 90 kg.

Table 5: Combination Therapy with Oral Agents and Two Types of Insulin in Patients with Type 2 Diabetes Mellitus [Mean (SD)]

Treatment duration 28-weeks	NovoLog Mix 70/30 + Metformin ± Pioglitazone	Insulin Glargine + Metformin ± Pioglitazone
Number of patients	117	116
HbA _{1c}		
Baseline mean (%)	9.7 ± 1.5 (117)	9.8 ± 1.4 (114)
End-of-study mean (± SD)	6.9 ± 1.2 (108)	7.4 ± 1.2 (114)
Mean change from baseline	-2.7 ± 1.6 (108)	-2.4 ± 1.5 (114)
Percentage of subjects reaching HbA _{1c} <7.0%	66%	40%
Total Daily Insulin Dose at end of study (U)	78 ± 40 (117)	51 ± 27 (116)
% of patients with severe hypoglycemia	0	0
% of minor hypoglycemia	43	16
Weight gain at end of study	5.4 ± 4.8 (117)	3.5 ± 4.5 (116)

15 REFERENCES

1. Raskin R, Allen E, Hollander P, et al. Initiating insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care*. 2005; 28:260-265.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

NovoLog Mix 70/30 is available in the following package sizes: each presentation contains 100 Units of insulin aspart per mL (U-100).

10 mL vials NDC 0169-3685-12

3 mL NovoLog Mix 70/30 FlexPen NDC 0169-3696-19

NovoLog Mix 70/30 vials and NovoLog Mix 70/30 FlexPen are latex free.

16.2 Recommended Storage

Unused NovoLog Mix 70/30 should be stored in a refrigerator between 2°C and 8°C (36°F to 46°F). Do not store in the freezer or directly adjacent to the refrigerator cooling element. **Do not freeze NovoLog Mix 70/30 or use NovoLog Mix 70/30 if it has been frozen.**

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. Open 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.

NovoLog Mix 70/30 FlexPen: Once a NovoLog Mix 70/30 FlexPen is punctured, it should be kept at temperatures below 30°C (86°F) for up to 14 days, but should not be exposed to excessive heat or sunlight. A NovoLog Mix 70/30 FlexPen in use must NOT be stored in the refrigerator. Keep the disposable NovoLog Mix 70/30 FlexPen away from direct heat and sunlight. An unpunctured NovoLog Mix 70/30 FlexPen can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep any unused NovoLog Mix 70/30 FlexPen in the carton so it will stay clean and protected from light.

These storage conditions are summarized in the following table:

Not in-use (unopened)

Room Temperature

(below 30°C [86°F]) Not in-use (unopened)

Refrigerated

(2°C - 8°C [36°F- 46°F]) In-use (opened)

Room Temperature

(below 30°C [86°F])

10 mL vial 28 days Until expiration date 28 days (refrigerated/room temperature)

3 mL NovoLog Mix 70/30 FlexPen 14 days Until expiration date 14 days (Do not refrigerate)

17 PATIENT COUNSELING INFORMATION

[see FDA-Approved Patient Labeling]

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 advantages of NovoLog Mix 70/30 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 for use of injection devices, and proper storage of insulin. See Patient Information supplied with the product. Patients should be informed that frequent, patient-performed blood glucose measurements are needed to achieve optimal glycemic control and avoid both hyper- and hypoglycemia, and diabetic ketoacidosis.

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 Mix 70/30 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 Mix 70/30 and any other insulin. **The prescription for NovoLog Mix 70/30 should be written clearly in order to avoid confusion with other insulin products, for example, NovoLog or Novolin 70/30.** In addition, the written prescription should clearly indicate the presentation, for example FlexPen or vial.

Rx only

Date of Issue: May 7, 2010

Version: 9

Novo Nordisk®, *NovoLog®*, *FlexPen®*, and *Novolin®* are registered trademarks of Novo Nordisk® A/S.

NovoLog® Mix 70/30 is covered by US Patent Nos. 5,547,930, 5,618,913, 5,834,422, 5,840,680, 5,866,538 and other patents pending.

FlexPen® is covered by US Patent Nos. 6,582,404, 6,004,297, 6,235,004 and other patents pending.

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www.novonordisk-us.com

R Human

Novolin® R

Regular,
Human Insulin Injection
(recombinant DNA origin) USP

100 units/mL

DESCRIPTION

Novolin® R Regular, Human Insulin Injection (rDNA origin) USP is a polypeptide hormone structurally identical to natural human insulin and is produced by rDNA technology, utilizing *Saccharomyces cerevisiae* (bakers' yeast) as the production organism. Human insulin has the empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5808 Da.

<< OLE Object: Picture (Metafile) >>

Figure 1. Structural formula of human insulin

Novolin R is a sterile, clear, aqueous, and colorless solution, that contains human insulin (rDNA origin) 100 units/mL, glycerin 16 mg/ml, metacresol 3 mg/mL and zinc chloride approximately 7 µg/mL. The pH is adjusted to 7.4. Hydrochloric acid 2N and/or sodium hydroxide 2N may be added to adjust pH.

CLINICAL PHARMACOLOGY

Insulin is a polypeptide hormone that controls the storage and metabolism of carbohydrates, proteins, and fats. This activity occurs primarily in the liver, in muscle, and in adipose tissues after binding of the insulin molecules to receptor sites on cellular plasma membranes.

Insulin promotes uptake of carbohydrates, proteins, and fats in most tissues. Also, insulin influences carbohydrate, protein, and fat metabolism by stimulating protein and free fatty acid synthesis, and by inhibiting release of free fatty acid from adipose cells. Insulin increases active glucose transport through muscle and adipose cellular membranes, and promotes conversion of intracellular glucose and free fatty acid to the appropriate storage forms (glycogen and triglyceride, respectively). Although the liver does not require active glucose transport, insulin increases hepatic glucose conversion to glycogen and suppresses hepatic glucose output. Even though the actions of exogenous insulin are identical to those of endogenous insulin, the ability to negatively affect hepatic glucose output differs on a unit per unit basis because a smaller quantity of an exogenous insulin dose reaches the portal vein.

Administered insulin, including Novolin R, substitutes for inadequate endogenous insulin secretion and partially corrects the disordered metabolism and inappropriate hyperglycemia of diabetes mellitus, which are caused by either a deficiency or a reduction in the biologic effectiveness of insulin. When administered in appropriate doses at prescribed intervals to patients with diabetes mellitus, Novolin R temporarily restores their ability to metabolize carbohydrates, proteins and fats.

Novolin R is a sterile, aqueous, and colorless solution of human insulin with a short duration of action. The pharmacologic effect of Novolin R begins approximately one-half (½) hour after subcutaneous administration. The effect is maximal between 2½ and 5 hours and terminates after approximately 8 hours. The onset of action of intravenous insulin is more rapid.

INDICATIONS AND USAGE

Novolin R is indicated for subcutaneous administration for the treatment of patients with diabetes mellitus, for the control of hyperglycemia. Treatment with Novolin R is as an adjunct to diet and exercise for lowering blood glucose in patients with Type 1 diabetes or in patients with Type 2 diabetes for whom oral antidiabetic therapy is inadequate.

Novolin R may be administered intravenously under proper medical supervision in a clinical setting for glycemic control. (See DOSAGE AND ADMINISTRATION and RECOMMENDED STORAGE.)

CONTRAINDICATIONS

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

WARNING

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, etc.), species (animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

Special care should be taken when the transfer is from a standard beef or mixed species insulin to a purified pork or human insulin. If a dosage adjustment is needed, it will usually become apparent either in the first few days or over a period of several weeks. Any change in treatment should be carefully monitored.

PRECAUTIONS

General

Hypoglycemia, hypokalemia, lipodystrophy and hypersensitivity are among the potential clinical adverse effects associated with the use of all insulins.

As with all insulin preparations, the time course of Novolin R action may vary in different individuals or at different times in the same individual and is dependent on dose, 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.

Novolin R should only be used if it is clear and colorless. Due to the risk of precipitation in some pump catheters, Novolin R is not recommended for use in insulin pumps.

Hypoglycemia and hypokalemia - As with all insulin preparations, hypoglycemic and hypokalemic reactions may be associated with the administration of Novolin R, particularly via the IV route. 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. Severe hypoglycemia can result in temporary or permanent impairment of brain function and death. 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 Novolin R or any other insulin is administered intravenously.

In certain cases, the nature and intensity of the warning symptoms of hypoglycemia may change. A few patients have reported that after being transferred to human insulin, the early warning symptoms for hypoglycemia had been less pronounced than they were with animal-source insulin.

Hyperglycemia and ketosis – Hyperglycemia, diabetic ketoacidosis, or diabetic coma may develop if the patient takes less Novolin R than needed to control blood glucose levels. This could be due to insulin demand during illness or infection, neglect of diet, omission or improper administration of prescribed insulin doses. A developing ketoacidosis will be revealed by urine tests which show large amounts of sugar and acetone. The symptoms of polydipsia, polyurea, loss of appetite, fatigue, dry skin and deep and rapid breathing come on gradually, usually over a period of some hours or days. Severe sustained hyperglycemia may result in diabetic coma or death.

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

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

Allergy - Local Allergy - As with other insulin therapy, patients may experience redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of Novolin R. 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.

Usage in Pregnancy

It is particularly important for patients to maintain good control of diabetes during pregnancy and special attention must be paid to diet, exercise and insulin regimens. Female patients should be advised to tell their physician if they intend to become, or if they become pregnant.

Information for Patients

Patients should be informed about potential risks and advantages of Novolin R 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 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.

Laboratory Tests

As with all insulin therapy, the therapeutic response to Novolin R should be monitored by

periodic blood glucose tests. Periodic measurement of glycosylated hemoglobin is recommended for the monitoring of long-term glycemic control. Urine ketones should be monitored frequently.

When Novolin R 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 reduce insulin requirement: oral hypoglycemic agents (OHA), octreotide, monoamine oxidase inhibitors (MAOI), non-selective beta-blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, alcohol, sulphonamide antibiotics, anabolic steroids, quinine, quinidine and alpha-adrenergic blocking agents.
- The following are examples of substances that may increase insulin requirement: oral contraceptives, thiazides, glucocorticoids, thyroid hormones and sympathomimetics, growth hormone, diazoxide, asparaginase and nicotinic acid.
- Beta-blocking agents may mask the symptoms of hypoglycemia and delay recovery from hypoglycemia.
- Alcohol may intensify and prolong the hypoglycemic effect of insulin.

Mixing of Insulins

- Novolin R should only be mixed as directed by the physician.
- Novolin R is a short-acting insulin and is often used in combination with intermediate- or long-acting insulins.
- The order of mixing and brand or model of syringe should be specified by the physician. A U-100 insulin syringe should always be used. Failure to use the correct syringe can lead to dosage errors.
- In general, when a longer-acting insulin (e.g. NPH insulin isophane suspensions) is mixed with short-acting soluble insulin (e.g., regular), the short-acting insulin should be drawn into the syringe first.

ADVERSE REACTIONS

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).*

Other - *Hypoglycemia, Hyperglycemia and ketosis (see PRECAUTIONS).*

OVERDOSAGE

Excess insulin may cause hypoglycemia and hypokalemia, particularly after 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

Novolin R, when used alone subcutaneously, is usually given three or more times daily before meals. The dosage and timing of Novolin R should be individualized and determined, based on the physician's advice, in accordance with the needs of the patient. Novolin R may also be used in combination with oral antidiabetic agents or longer-acting insulin products to suit the needs of the individual patients. The injection of Novolin R should be followed by a meal within approximately 30 minutes of administration.

The average range of total daily insulin requirement for maintenance therapy in insulin-treated patients lies between 0.5 and 1.0 IU/kg. However, in pre-pubertal children it usually varies from 0.7 to 1.0 IU/kg, but can be much lower during the period of partial remission. In severe insulin resistance, e.g. during puberty or due to obesity, the daily insulin requirement may be substantially higher. Initial dosages for Type 2 diabetes patients are often lower, e.g. 0.2 to 0.4 IU/kg/day.

Novolin R should be administered by subcutaneous injection in the abdominal wall, the thigh, the gluteal region or in the upper arm. Subcutaneous injection into the abdominal wall ensures a faster absorption than from other injection sites. Injection into a lifted skin fold minimizes the risk of intramuscular injection. Injection 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.

Intramuscular and intravenous administrations of Novolin R are possible under medical supervision with close monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia.

For intravenous use, Novolin R should be used at concentrations from 0.05 U/mL to 1.0 U/mL 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.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Never use Novolin R if it has become viscous (thickened) or cloudy; use it only if it is clear and colorless. **Novolin R should not be used after the printed expiration date.**

RECOMMENDED STORAGE

Novolin R vials, Novolin[®] R PenFill[®] cartridges, and Novolin[®] R InnoLet[®] prefilled insulin syringes should be stored in a cold (36° - 46°F [2° - 8°C]) place, preferably in a refrigerator, but not in the freezer. **Do not freeze.** Keep Novolin R vials, Novolin R PenFill cartridges and Novolin R InnoLet in their cartons so that they will stay clean and protected from light. They should not be exposed to heat or sunlight. A Novolin R vial in use can be kept unrefrigerated as long as it is kept as cool as possible and away from heat or sunlight. A Novolin R PenFill cartridge and Novolin R InnoLet in use should not be refrigerated but should be kept as cool as possible (below 86°F [30°C]) and away from direct heat and light. Unrefrigerated Novolin R PenFill cartridges and Novolin R InnoLet must be discarded 28 days after the first use, even if they still contain Novolin R insulin.

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.

Never use insulin after the expiration date which is printed on the label and carton.

HOW SUPPLIED

Novolin R, Regular, Human Insulin Injection (rDNA origin) USP, 100 units/mL, is supplied as follows:

- 10 mL vial NDC 0169-1833-11
- 3 mL PenFill cartridges* NDC 0169-3473-18
- 3 mL Novolin R InnoLet NDC 0169-2313-21

*Novolin R PenFill 3 mL cartridges are designed for use with Novo Nordisk 3 mL PenFill cartridge compatible insulin delivery devices, the NovoPen® 3 PenMate® and with NovoFine® disposable needles.

Date of issue: October 21, 2005

For information contact: Novo Nordisk Inc., Princeton, NJ 08540
[1-800-727-6500](tel:1-800-727-6500)
www.novonordisk-us.com

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

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Victoza safely and effectively. See full prescribing information for Victoza.

**Victoza® (liraglutide [rDNA origin] injection), solution for subcutaneous use
Initial U.S. Approval: 2010**

.....CONTRAINDICATIONS.....

Do not use in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4).

.....WARNINGS AND PRECAUTIONS.....

- Thyroid C-cell tumors in animals: Human relevance unknown. Counsel patients

regarding the risk of medullary thyroid carcinoma and the symptoms of thyroid tumors (5.1).

- Pancreatitis: In clinical trials, there were more cases of pancreatitis among Victoza-treated patients than among comparator-treated patients. If pancreatitis is suspected, Victoza and other potentially suspect drugs should be discontinued. Victoza should not be restarted if pancreatitis is confirmed. Use with caution in patients with a history of pancreatitis (5.2).

- Serious hypoglycemia: Can occur when Victoza is used with an insulin secretagogue (e.g. a sulfonylurea). Consider lowering the dose of the insulin secretagogue to reduce the risk of hypoglycemia (5.3).

- Renal Impairment: Has been reported postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. Use caution when initiating or escalating doses of Victoza in patients with renal impairment (5.4).

- Macrovascular outcomes: There have been no studies establishing conclusive evidence of macrovascular risk reduction with Victoza or any other antidiabetic drug (5.5).

.....**ADVERSE REACTIONS**.....

- The most common adverse reactions, reported in $\geq 5\%$ of patients treated with Victoza and more commonly than in patients treated with placebo, are: headache, nausea, diarrhea and anti-liraglutide antibody formation (6).

- Immunogenicity-related events, including urticaria, were more common among Victoza-treated patients (0.8%) than among comparator-treated patients (0.4%) in clinical trials (6).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at [1-877-484-2869](tel:1-877-484-2869) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----**DRUG INTERACTIONS**-----

- Victoza delays gastric emptying. May impact absorption of concomitantly administered oral medications. Use caution (7).

.....**USE IN SPECIFIC POPULATIONS**.....

- There are no data in patients below 18 years of age (8.4).
- Use with caution in patients with renal or hepatic impairment. Limited data (8.6, 8.7).

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Medication Guide.

Revised: 5/2011
WARNING: RISK OF THYROID C-CELL TUMORS

See full prescribing information for complete boxed warning.

- **Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in rodents. It is unknown whether Victoza causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies (5.1).**
- **Victoza is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) (5.1).**

.....**RECENT MAJOR CHANGES**.....

Warnings and Precautions: Renal Impairment (5.4)
05/2011

.....**INDICATIONS AND USAGE**.....

Victoza is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1).

Important Limitations of Use (1.1):

- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise (5.1).
- Has not been studied sufficiently in patients with a history of pancreatitis. Use caution (5.2).
- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
- Has not been studied in combination with insulin.

.....**DOSAGE AND ADMINISTRATION**.....

- Administer once daily at any time of day, independently of meals (2).
- Inject subcutaneously in the abdomen, thigh or upper arm (2).
- The injection site and timing can be changed without dose adjustment (2).
- Initiate at 0.6 mg per day for one week. This dose is intended to reduce gastrointestinal symptoms during initial titration, and is not effective for glycemic control. After one week, increase the dose to 1.2 mg. If the 1.2 mg dose does not result in acceptable glycemic control, the dose can be increased to 1.8 mg (2).
- When initiating Victoza, consider reducing the dose of concomitantly-administered insulin secretagogues to reduce the risk of hypoglycemia (2).

.....**DOSAGE FORMS AND STRENGTHS**.....

- Solution for subcutaneous injection, pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg (6 mg/mL, 3 mL) (3).

FULL PRESCRIBING INFORMATION: CONTENTS*
BOXED WARNING: RISK OF THYROID C-CELL TUMORS

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF THYROID C-CELL TUMORS

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors [see *Contraindications (4)*, *Warnings and Precautions (5.1)* and *Nonclinical Toxicology (13.1)*].

1 INDICATIONS AND USAGE

Victoza is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

1.1 Important Limitations of Use

§ Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.

§ In clinical trials of Victoza, there were more cases of pancreatitis with Victoza than with comparators. Victoza has not been studied sufficiently in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis while using Victoza. Use with caution in patients with a history of pancreatitis.

§ Victoza is not a substitute for insulin. Victoza should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be

effective in these settings.

§ The concurrent use of Victoza and insulin has not been studied.

2 DOSAGE AND ADMINISTRATION

Victoza can be administered once daily at any time of day, independently of meals, and can be injected subcutaneously in the abdomen, thigh or upper arm. The injection site and timing can be changed without dose adjustment.

For all patients, Victoza should be initiated with a dose of 0.6 mg per day for one week. The 0.6 mg dose is a starting dose intended to reduce gastrointestinal symptoms during initial titration, and is not effective for glycemic control. After one week at 0.6 mg per day, the dose should be increased to 1.2 mg. If the 1.2 mg dose does not result in acceptable glycemic control, the dose can be increased to 1.8 mg.

When initiating Victoza, consider reducing the dose of concomitantly administered insulin secretagogues (such as sulfonylureas) to reduce the risk of hypoglycemia [*see Warnings and Precautions (5.3) and Adverse Reactions (6)*].

Victoza solution should be inspected prior to each injection, and the solution should be used only if it is clear, colorless, and contains no particles.

3 DOSAGE FORMS AND STRENGTHS

Solution for subcutaneous injection, pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg (6 mg/mL, 3 mL).

4 CONTRAINDICATIONS

Victoza is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-cell Tumors

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice [*see Nonclinical Toxicology (13.1)*]. Malignant thyroid C-cell carcinomas were detected in rats and mice. A statistically significant increase in cancer was observed in rats receiving liraglutide at 8-times clinical exposure compared to controls. It is unknown whether Victoza will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies [*see Boxed Warning, Contraindications (4)*].

In the clinical trials, there have been 4 reported cases of thyroid C-cell hyperplasia among Victoza-treated patients and 1 case in a comparator-treated patient (1.3 vs. 0.6 cases per 1000 patient-years). One additional case of thyroid C-cell hyperplasia in a Victoza-treated patient and 1 case of MTC in a comparator-treated patient have subsequently been reported. This comparator-treated patient with MTC had pre-treatment serum calcitonin concentrations >1000 ng/L suggesting pre-existing disease. All of these cases were diagnosed after thyroidectomy, which was prompted by abnormal

results on routine, protocol-specified measurements of serum calcitonin. Four of the five liraglutide-treated patients had elevated calcitonin concentrations at baseline and throughout the trial. One liraglutide and one non-liraglutide-treated patient developed elevated calcitonin concentrations while on treatment.

Calcitonin, a biological marker of MTC, was measured throughout the clinical development program. The serum calcitonin assay used in the Victoza clinical trials had a lower limit of quantification (LLOQ) of 0.7 ng/L and the upper limit of the reference range was 5.0 ng/L for women and 8.4 ng/L for men. At Weeks 26 and 52 in the clinical trials, adjusted mean serum calcitonin concentrations were higher in Victoza-treated patients compared to placebo-treated patients but not compared to patients receiving active comparator. At these timepoints, the adjusted mean serum calcitonin values (~ 1.0 ng/L) were just above the LLOQ with between-group differences in adjusted mean serum calcitonin values of approximately 0.1 ng/L or less. Among patients with pre-treatment serum calcitonin below the upper limit of the reference range, shifts to above the upper limit of the reference range which persisted in subsequent measurements occurred most frequently among patients treated with Victoza 1.8 mg/day. In trials with on-treatment serum calcitonin measurements out to 5-6 months, 1.9% of patients treated with Victoza 1.8 mg/day developed new and persistent calcitonin elevations above the upper limit of the reference range compared to 0.8-1.1% of patients treated with control medication or the 0.6 and 1.2 mg doses of Victoza. In trials with on-treatment serum calcitonin measurements out to 12 months, 1.3% of patients treated with Victoza 1.8 mg/day had new and persistent elevations of calcitonin from below or within the reference range to above the upper limit of the reference range, compared to 0.6%, 0% and 1.0% of patients treated with Victoza 1.2 mg, placebo and active control, respectively. Otherwise, Victoza did not produce consistent dose-dependent or time-dependent increases in serum calcitonin.

Patients with MTC usually have calcitonin values >50 ng/L. In Victoza clinical trials, among patients with pre-treatment serum calcitonin <50 ng/L, one Victoza-treated patient and no comparator-treated patients developed serum calcitonin >50 ng/L. The Victoza-treated patient who developed serum calcitonin >50 ng/L had an elevated pre-treatment serum calcitonin of 10.7 ng/L that increased to 30.7 ng/L at Week 12 and 53.5 ng/L at the end of the 6-month trial. Follow-up serum calcitonin was 22.3 ng/L more than 2.5 years after the last dose of Victoza. The largest increase in serum calcitonin in a comparator-treated patient was seen with glimepiride in a patient whose serum calcitonin increased from 19.3 ng/L at baseline to 44.8 ng/L at Week 65 and 38.1 ng/L at Week 104. Among patients who began with serum calcitonin <20 ng/L, calcitonin elevations to >20 ng/L occurred in 0.7% of Victoza-treated patients, 0.3% of placebo-treated patients, and 0.5% of active-comparator-treated patients, with an incidence of 1.1% among patients treated with 1.8 mg/day of Victoza. The clinical significance of these findings is unknown.

Counsel patients regarding the risk for MTC and the symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea or persistent hoarseness). It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate the potential risk of MTC, and such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Patients with thyroid nodules noted on physical examination or neck imaging obtained for other reasons should be referred to an endocrinologist for further evaluation. Although routine monitoring of serum calcitonin is of uncertain value in patients treated with

Victoza, if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation.

5.2 Pancreatitis

In clinical trials of Victoza, there were 7 cases of pancreatitis among Victoza-treated patients and 1 case among comparator-treated patients (2.2 vs. 0.6 cases per 1000 patient-years). Five cases with Victoza were reported as acute pancreatitis and two cases with Victoza were reported as chronic pancreatitis. In one case in a Victoza-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. One additional case of pancreatitis has subsequently been reported in a Victoza-treated patient. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse. There are no conclusive data establishing a risk of pancreatitis with Victoza treatment. After initiation of Victoza, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, Victoza and other potentially suspect medications should be discontinued promptly, confirmatory tests should be performed and appropriate management should be initiated. If pancreatitis is confirmed, Victoza should not be restarted. Use with caution in patients with a history of pancreatitis.

5.3 Use with Medications Known to Cause Hypoglycemia

Patients receiving Victoza in combination with an insulin secretagogue (e.g., sulfonylurea) may have an increased risk of hypoglycemia. In the clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 7 Victoza-treated patients and in two comparator-treated patients. Six of these 7 patients treated with Victoza were also taking a sulfonylurea. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea or other insulin secretagogues [*see Adverse Reactions (6.1)*].

5.4 Renal Impairment

Victoza has not been found to be directly nephrotoxic in animal studies or clinical trials. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in Victoza-treated patients [*see Adverse Reactions (6.2)*]. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration [*see Adverse Reactions (6.1)*]. Some of the reported events occurred in patients receiving one or more medications known to affect renal

function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including Victoza. Use caution when initiating or escalating doses of Victoza in patients with renal impairment [*see Use in Specific Populations (8.6)*].

5.5 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Victoza or any other antidiabetic drug.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of Victoza was evaluated in a 52-week monotherapy trial and in five 26-week, add-on combination therapy trials. In the monotherapy trial, patients were treated with Victoza 1.2 mg daily, Victoza 1.8 mg daily, or glimepiride 8 mg daily. In the add-on to metformin trial, patients were treated with Victoza 0.6 mg, Victoza 1.2 mg, Victoza 1.8 mg, placebo, or glimepiride 4 mg. In the add-on to glimepiride trial, patients were treated with Victoza 0.6 mg, Victoza 1.2 mg, Victoza 1.8 mg, placebo, or rosiglitazone 4 mg. In the add-on to metformin + glimepiride trial, patients were treated with Victoza 1.8 mg, placebo, or insulin glargine. In the add-on to metformin + rosiglitazone trial, patients were treated with Victoza 1.2 mg, Victoza 1.8 mg or placebo [see *Clinical Studies (14)*].

Withdrawals

The incidence of withdrawal due to adverse events was 7.8% for Victoza-treated patients and 3.4% for comparator-treated patients in the five controlled trials of 26 weeks duration or longer. This difference was driven by withdrawals due to gastrointestinal adverse reactions, which occurred in 5.0% of Victoza-treated patients and 0.5% of comparator-treated patients. The most common adverse reactions leading to withdrawal for Victoza-treated patients were nausea (2.8% versus 0% for comparator) and vomiting (1.5% versus 0.1% for comparator). Withdrawal due to gastrointestinal adverse events mainly occurred during the first 2-3 months of the trials.

Tables 1, 2 and 3 summarize the adverse events reported in $\geq 5\%$ of Victoza-treated patients in the six controlled trials of 26 weeks duration or longer.

Table 1 Adverse events reported in $\geq 5\%$ of Victoza-treated patients or $\geq 5\%$ of glimepiride-treated patients: 52-week monotherapy trial

All Victoza

		N = 497 Glimepiride			
		N = 248			
Adverse Event Term	(%)	(%)	(%)		
Nausea	28.4	8.5			
Diarrhea	17.1	8.9			
Vomiting	10.9	3.6			
Constipation	9.9	4.8			
Upper Respiratory Tract Infection			9.5	5.6	
Headache	9.1	9.3			
Influenza	7.4	3.6			
Urinary Tract Infection	6.0	4.0			
Dizziness	5.8	5.2			
Sinusitis	5.6	6.0			
Nasopharyngitis	5.2	5.2			
Back Pain	5.0	4.4			

Hypertension 3.0 6.0

Table 2 Adverse events reported in ≥5% of Victoza-treated patients and occurring more frequently with Victoza compared to placebo: 26-week combination therapy trials

Add-on to Metformin Trial

All Victoza + Metformin

N = 724 Placebo + Metformin

N = 121 Glimepiride +

Metformin

N = 242

Adverse Event Term	(%)	(%)	(%)
Nausea	15.2	4.1	3.3
Diarrhea	10.9	4.1	3.7
Headache	9.0	6.6	9.5
Vomiting	6.5	0.8	0.4

Add-on to Glimepiride Trial

All Victoza +

Glimepiride

N = 695 Placebo +

Glimepiride

N = 114 Rosiglitazone +

Glimepiride

N = 231

Adverse Event Term	(%)	(%)	(%)
Nausea	7.5	1.8	2.6
Diarrhea	7.2	1.8	2.2
Constipation	5.3	0.9	1.7
Dyspepsia	5.2	0.9	2.6

Add-on to Metformin + Glimepiride

Victoza 1.8 + Metformin + Glimepiride

N = 230 Placebo +

Metformin + Glimepiride

N = 114 Glargine +

Metformin +

Glimepiride

N = 232

Adverse Event Term	(%)	(%)	(%)
Nausea	13.9	3.5	1.3
Diarrhea	10.0	5.3	1.3
Headache	9.6	7.9	5.6
Dyspepsia	6.5	0.9	1.7
Vomiting	6.5	3.5	0.4

Add-on to Metformin + Rosiglitazone

All Victoza +

Metformin + Rosiglitazone

N = 355 Placebo +

Metformin + Rosiglitazone

N = 175

Adverse Event Term	(%)	(%)
Nausea	34.6	8.6
Diarrhea	14.1	6.3
Vomiting	12.4	2.9
Decreased Appetite	9.3	1.1
Anorexia	9.0	0.0
Headache	8.2	4.6
Constipation	5.1	1.1
Fatigue	5.1	1.7

Table 3 Treatment-Emergent Adverse Events in 26 Week Open-Label Trial versus Exenatide

(Adverse events with frequency $\geq 5\%$ and occurring more frequently with Victoza compared to exenatide are listed)

Victoza

1.8 mg once daily

+ metformin and/or sulfonylurea

N = 235 Exenatide

10 mcg twice daily

+ metformin and/or sulfonylurea

N = 232

Preferred Term (%) (%)

Diarrhea	12.3	12.1
Dyspepsia	8.9	4.7
Constipation	5.1	2.6

Gastrointestinal adverse events

In the five clinical trials of 26 weeks duration or longer, gastrointestinal adverse events were reported in 41% of Victoza-treated patients and were dose-related. Gastrointestinal adverse events occurred in 17% of comparator-treated patients. Events that occurred more commonly among Victoza-treated patients included nausea, vomiting, diarrhea, dyspepsia and constipation. In a 26-week study of Victoza versus exenatide, both in combination with metformin and/or sulfonylurea [see *Clinical Studies (14.2)*] overall gastrointestinal adverse event incidence rates, including nausea, were similar in patients treated with Victoza and exenatide.

In five clinical trials of 26 weeks duration or longer, the percentage of patients who reported nausea declined over time. Approximately 13% of Victoza-treated patients and 2% of comparator-treated patients reported nausea during the first 2 weeks of treatment.

In a 26 week study of Victoza versus exenatide, both in combination with metformin and/or sulfonylurea [see *Clinical Studies (14.2)*], the proportion of patients with nausea also declined over time.

Immunogenicity

Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with Victoza may develop anti-liraglutide antibodies. Approximately 50-70% of Victoza-treated patients in the five clinical trials of 26 weeks duration or longer were tested for the presence of anti-liraglutide antibodies at the end of treatment. Low titers (concentrations not requiring dilution of serum) of anti-liraglutide antibodies were detected in 8.6% of these Victoza-treated patients. Sampling was not performed uniformly across all patients in the clinical trials, and this may have resulted in an underestimate of the actual percentage of patients who developed antibodies. Cross-reacting anti-liraglutide antibodies to native glucagon-like peptide-1 (GLP-1) occurred in 6.9% of the Victoza-treated patients in the 52-week monotherapy trial and in 4.8% of the Victoza-treated patients in the 26-week add-on combination therapy trials. These cross-reacting antibodies were not tested for neutralizing effect against native GLP-1, and thus the potential for clinically significant neutralization of native GLP-1 was not assessed. Antibodies that had a neutralizing effect on liraglutide in an *in vitro* assay occurred in 2.3% of the Victoza-treated patients in the 52-week monotherapy trial and in 1.0% of the Victoza-treated patients in the 26-week add-on combination therapy trials.

Among Victoza-treated patients who developed anti-liraglutide antibodies, the most common category of adverse events was that of infections, which occurred among 40% of these patients compared to 36%, 34% and 35% of antibody-negative Victoza-treated, placebo-treated and active-control-treated patients, respectively. The specific infections which occurred with greater frequency among Victoza-treated antibody-positive patients were primarily nonserious upper respiratory tract infections, which occurred among 11% of Victoza-treated antibody-positive patients; and among 7%, 7% and 5% of antibody-negative Victoza-treated, placebo-treated and active-control-treated patients,

respectively. Among Victoza-treated antibody-negative patients, the most common category of adverse events was that of gastrointestinal events, which occurred in 43%, 18% and 19% of antibody-negative Victoza-treated, placebo-treated and active-control-treated patients, respectively. Antibody formation was not associated with reduced efficacy of Victoza when comparing mean HbA_{1c} of all antibody-positive and all antibody-negative patients. However, the 3 patients with the highest titers of anti-liraglutide antibodies had no reduction in HbA_{1c} with Victoza treatment.

In clinical trials of Victoza, events from a composite of adverse events potentially related to immunogenicity (e.g. urticaria, angioedema) occurred among 0.8% of Victoza-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for Victoza-treated patients. Patients who developed anti-liraglutide antibodies were not more likely to develop events from the immunogenicity events composite than were patients who did not develop anti-liraglutide antibodies.

Injection site reactions

Injection site reactions (e.g., injection site rash, erythema) were reported in approximately 2% of Victoza-treated patients in the five clinical trials of at least 26 weeks duration. Less than 0.2% of Victoza-treated patients discontinued due to injection site reactions.

Papillary thyroid carcinoma

In clinical trials of Victoza, there were 6 reported cases of papillary thyroid carcinoma in patients treated with Victoza and 1 case in a comparator-treated patient (1.9 vs. 0.6 cases per 1000 patient-years). Most of these papillary thyroid carcinomas were <1 cm in greatest diameter and were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings on protocol-specified screening with serum calcitonin or thyroid ultrasound.

Hypoglycemia

In the clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 7 Victoza-treated patients (2.6 cases per 1000 patient-years) and in two comparator-treated patients. Six of these 7 patients treated with Victoza were also taking a sulfonylurea. One other patient was taking Victoza in combination with metformin but had another likely explanation for the hypoglycemia (this event occurred during hospitalization and after insulin infusion) (Table 4). Two additional cases of hypoglycemia requiring the assistance of another person for treatment have subsequently been reported in patients who were not taking a concomitant sulfonylurea. Both patients were receiving Victoza, one as monotherapy and the other in combination with metformin. Both patients had another likely explanation for the hypoglycemia (one received insulin during a frequently-sampled intravenous glucose tolerance test, and the other had intracranial hemorrhage and uncertain food intake).

Table 4 Incidence (%) and Rate (episodes/patient year) of Hypoglycemia in the 52-Week Monotherapy Trial and in the 26-Week Combination Therapy Trials

	Victoza Treatment	Active Comparator	Placebo Comparator
Monotherapy	Victoza (N = 497)	Glimepiride (N = 248)	None
Patient not able to self-treat	0	0	-
Patient able to self-treat	9.7 (0.24)	25.0 (1.66)	-

Not classified 1.2 (0.03) 2.4 (0.04) -

Add-on to Metformin Victoza +

Metformin

(N = 724) **Glimepiride +**

Metformin

(N = 242) **Placebo +**

Metformin

(N = 121)

Patient not able to self-treat 0.1 (0.001) 0 0

Patient able to self-treat 3.6 (0.05) 22.3 (0.87) 2.5 (0.06)

Add-on to Glimepiride Victoza +

Glimepiride

(N = 695) **Rosiglitazone + Glimepiride**

(N = 231) **Placebo +**

Glimepiride

(N = 114)

Patient not able to self-treat 0.1 (0.003) 0 0

Patient able to self-treat 7.5 (0.38) 4.3 (0.12) 2.6 (0.17)

Not classified 0.9 (0.05) 0.9 (0.02) 0

Add-on to Metformin + Rosiglitazone Victoza +

Metformin +

Rosiglitazone

(N = 355)

None Placebo +

Metformin + Rosiglitazone

(N = 175)

Patient not able to self-treat 0 - 0

Patient able to self-treat 7.9 (0.49) - 4.6 (0.15)

Not classified 0.6 (0.01) - 1.1 (0.03)

Add-on to Metformin + Glimepiride Victoza +

Metformin +

Glimepiride

(N = 230) **Insulin glargine + Metformin +**

Glimepiride

(N = 232) **Placebo +**

Metformin + Glimepiride

(N = 114)

Patient not able to self-treat	2.2 (0.06)	0	0
Patient able to self-treat	27.4 (1.16)	28.9 (1.29)	16.7 (0.95)
Not classified	0	1.7 (0.04)	0

In a pooled analysis of clinical trials, the incidence rate (per 1,000 patient-years) for malignant neoplasms (based on investigator-reported events, medical history, pathology reports, and surgical reports from both blinded and open-label study periods) was 10.9 for Victoza, 6.3 for placebo, and 7.2 for active comparator. After excluding papillary thyroid carcinoma events [see *Adverse Reactions (6.1)*], no particular cancer cell type predominated. Seven malignant neoplasm events were reported beyond 1 year of exposure to study medication, six events among Victoza-treated patients (4 colon, 1 prostate and 1 nasopharyngeal), no events with placebo and one event with active comparator (colon). Causality has not been established.

Laboratory Tests

In the five clinical trials of at least 26 weeks duration, mildly elevated serum bilirubin concentrations (elevations to no more than twice the upper limit of the reference range) occurred in 4.0% of Victoza-treated patients, 2.1% of placebo-treated patients and 3.5% of active-comparator-treated patients. This finding was not accompanied by abnormalities in other liver tests. The significance of this isolated finding is unknown.

6.2 Post-Marketing Experience

The following additional adverse reactions have been reported during post-approval use of Victoza. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal: nausea, vomiting and diarrhea sometimes resulting in dehydration. [see *Warnings and Precautions (5.4)* and *Patient Counseling Information (17.2)*]

Renal and Urinary Disorders: increased serum creatinine, acute renal failure or worsening of chronic renal failure, which may sometimes require hemodialysis. [see *Warnings and Precautions (5.4)* and *Patient Counseling Information (17.2)*]

7 DRUG INTERACTIONS

7.1 Oral Medications

Victoza causes a delay of gastric emptying, and thereby has the potential to impact the

absorption of concomitantly administered oral medications. In clinical pharmacology trials, Victoza did not affect the absorption of the tested orally administered medications to any clinically relevant degree. Nonetheless, caution should be exercised when oral medications are concomitantly administered with Victoza.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies of Victoza in pregnant women. Victoza should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Liraglutide has been shown to be teratogenic in rats at or above 0.8 times the human systemic exposures resulting from the maximum recommended human dose (MRHD) of 1.8 mg/day based on plasma area under the time-concentration curve (AUC). Liraglutide has been shown to cause reduced growth and increased total major abnormalities in rabbits at systemic exposures below human exposure at the MRHD based on plasma AUC.

Female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide beginning 2 weeks before mating through gestation day 17 had estimated systemic exposures 0.8-, 3-, and 11-times the human exposure at the MRHD based on plasma AUC comparison. The number of early embryonic deaths in the 1 mg/kg/day group increased slightly. Fetal abnormalities and variations in kidneys and blood vessels, irregular ossification of the skull, and a more complete state of ossification occurred at all doses. Mottled liver and minimally kinked ribs occurred at the highest dose. The incidence of fetal malformations in liraglutide-treated groups exceeding concurrent and historical controls were misshapen oropharynx and/or narrowed opening into larynx at 0.1 mg/kg/day and umbilical hernia at 0.1 and 0.25 mg/kg/day.

Pregnant rabbits given subcutaneous doses of 0.01, 0.025 and 0.05 mg/kg/day liraglutide from gestation day 6 through day 18 inclusive, had estimated systemic exposures less than the human exposure at the MRHD of 1.8 mg/day at all doses, based on plasma AUC. Liraglutide decreased fetal weight and dose-dependently increased the incidence of total major fetal abnormalities at all doses. The incidence of malformations exceeded concurrent and historical controls at 0.01 mg/kg/day (kidneys, scapula), ≥ 0.01 mg/kg/day (eyes, forelimb), 0.025 mg/kg/day (brain, tail and sacral vertebrae, major blood vessels and heart, umbilicus), ≥ 0.025 mg/kg/day (sternum) and at 0.05 mg/kg/day (parietal bones, major blood vessels). Irregular ossification and/or skeletal abnormalities occurred in the skull and jaw, vertebrae and ribs, sternum, pelvis, tail, and scapula; and dose-dependent minor skeletal variations were observed. Visceral abnormalities occurred in blood vessels, lung, liver, and esophagus. Bilobed or bifurcated gallbladder was seen in all treatment groups, but not in the control group.

In pregnant female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide from gestation day 6 through weaning or termination of nursing on lactation day 24, estimated systemic exposures were 0.8-, 3-, and 11-times human exposure at the MRHD of 1.8 mg/day, based on plasma AUC. A slight delay in parturition was observed in the majority of treated rats. Group mean body weight of neonatal rats from liraglutide-treated dams was lower than neonatal rats from control group dams. Bloody scabs and agitated behavior occurred in male rats descended from dams treated with 1 mg/kg/day liraglutide. Group mean body weight from birth to postpartum day 14 trended lower in F₂ generation rats descended from liraglutide-treated rats compared to

F₂ generation rats descended from controls, but differences did not reach statistical significance for any group.

8.3 Nursing Mothers

It is not known whether Victoza is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for liraglutide in animal studies, a decision should be made whether to discontinue nursing or to discontinue Victoza, taking into account the importance of the drug to the mother. In lactating rats, liraglutide was excreted unchanged in milk at concentrations approximately 50% of maternal plasma concentrations.

8.4 Pediatric Use

Safety and effectiveness of Victoza have not been established in pediatric patients. Victoza is not recommended for use in pediatric patients.

8.5 Geriatric Use

In the Victoza clinical trials, a total of 797 (20%) of the patients were 65 years of age and over and 113 (2.8%) were 75 years of age and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

There is limited experience with Victoza in patients with mild, moderate, and severe renal impairment, including endstage renal disease. However, there have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis [*see Warnings and Precautions (5.4) and Adverse Reactions (6.2)*]. Victoza should be used with caution in this patient population. No dose adjustment of Victoza is recommended for patients with renal impairment [*see Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

There is limited experience in patients with mild, moderate or severe hepatic impairment. Therefore, Victoza should be used with caution in this patient population. No dose adjustment of Victoza is recommended for patients with hepatic impairment [*see Clinical Pharmacology (12.3)*].

8.8 Gastroparesis

Victoza slows gastric emptying. Victoza has not been studied in patients with pre-existing gastroparesis.

10 OVERDOSAGE

In a clinical trial, one patient with type 2 diabetes experienced a single overdose of Victoza 17.4 mg subcutaneous (10 times the maximum recommended dose). Effects of the overdose included severe nausea and vomiting requiring hospitalization. No hypoglycemia was reported. The patient recovered without complications. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

11 DESCRIPTION

Victoza contains liraglutide, an analog of human GLP-1 and acts as a GLP-1 receptor agonist. The peptide precursor of liraglutide, produced by a process that includes expression of recombinant DNA in *Saccharomyces cerevisiae*, has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34. Liraglutide is made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on the remaining lysine residue at position 26 of the peptide precursor. The molecular formula of liraglutide is $C_{172}H_{265}N_{43}O_{51}$ and the molecular weight is 3751.2 Daltons. The structural formula (Figure 1) is:

<< OLE Object: Picture (Metafile) >>

Figure 1 Structural Formula of liraglutide

Victoza is a clear, colorless solution. Each 1 mL of Victoza solution contains 6 mg of liraglutide. Each pre-filled pen contains a 3 mL solution of Victoza equivalent to 18 mg liraglutide (free-base, anhydrous) and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Liraglutide is an acylated human Glucagon-Like Peptide-1 (GLP-1) receptor agonist with 97% amino acid sequence homology to endogenous human GLP-1(7-37). GLP-1(7-37) represents <20% of total circulating endogenous GLP-1. Like GLP-1(7-37), liraglutide activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylyl cyclase by the stimulatory G-protein, G_s, in pancreatic beta cells. Liraglutide increases intracellular cyclic AMP (cAMP) leading to insulin release in the presence of elevated glucose concentrations. This insulin secretion subsides as blood glucose concentrations decrease and approach euglycemia. Liraglutide also decreases glucagon secretion in a glucose-dependent manner. The mechanism of blood glucose lowering also involves a delay in gastric emptying.

GLP-1(7-37) has a half-life of 1.5-2 minutes due to degradation by the ubiquitous endogenous enzymes, dipeptidyl peptidase IV (DPP-IV) and neutral endopeptidases (NEP). Unlike native GLP-1, liraglutide is stable against metabolic degradation by both peptidases and has a plasma half-life of 13 hours after subcutaneous administration. The pharmacokinetic profile of liraglutide, which makes it suitable for once daily administration, is a result of self-association that delays absorption, plasma protein binding and stability against metabolic degradation by DPP-IV and NEP.

12.2 Pharmacodynamics

Victoza's pharmacodynamic profile is consistent with its pharmacokinetic profile observed after single subcutaneous administration as Victoza lowered fasting, premeal and postprandial glucose throughout the day [see *Clinical Pharmacology (12.3)*].

Fasting and postprandial glucose was measured before and up to 5 hours after a standardized meal after treatment to steady state with 0.6, 1.2 and 1.8 mg Victoza or placebo. Compared to placebo, the postprandial plasma glucose AUC_{0-300min} was 35% lower after Victoza 1.2 mg and 38% lower after Victoza 1.8 mg.

Glucose-dependent insulin secretion

The effect of a single dose of 7.5 mcg/kg (~ 0.7 mg) Victoza on insulin secretion rates (ISR) was investigated in 10 patients with type 2 diabetes during graded glucose infusion. In these patients, on average, the ISR response was increased in a glucose-dependent manner (Figure 2).

<< OLE Object: Picture (Enhanced Metafile) >> **Figure 2 Mean Insulin Secretion Rate (ISR) versus Glucose Concentration Following Single-Dose Victoza 7.5 mcg/kg (~ 0.7 mg) or Placebo in Patients with Type 2 Diabetes (N=10) During Graded Glucose Infusion**

Glucagon secretion

Victoza lowered blood glucose by stimulating insulin secretion and lowering glucagon secretion. A single dose of Victoza 7.5 mcg/kg (~ 0.7 mg) did not impair glucagon response to low glucose concentrations.

Gastric emptying

Victoza causes a delay of gastric emptying, thereby reducing the rate at which postprandial glucose appears in the circulation.

Cardiac Electrophysiology (QTc)

The effect of Victoza on cardiac repolarization was tested in a QTc study. Victoza at steady state concentrations with daily doses up to 1.8 mg did not produce QTc prolongation.

12.3 Pharmacokinetics

Absorption - Following subcutaneous administration, maximum concentrations of liraglutide are achieved at 8-12 hours post dosing. The mean peak (C_{max}) and total (AUC) exposures of liraglutide were 35 ng/mL and 960 ng·h/mL, respectively, for a subcutaneous single dose of 0.6 mg. After subcutaneous single dose administrations, C_{max} and AUC of liraglutide increased proportionally over the therapeutic dose range of 0.6 mg to 1.8 mg. At 1.8 mg Victoza, the average steady state concentration of liraglutide over 24 hours was approximately 128 ng/mL. $AUC_{0-\infty}$ was equivalent between upper arm and abdomen, and between upper arm and thigh. $AUC_{0-\infty}$ from thigh was 22% lower than that from abdomen. However, liraglutide exposures were considered comparable among these three subcutaneous injection sites. Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55%.

Distribution - The mean apparent volume of distribution after subcutaneous administration of Victoza 0.6 mg is approximately 13 L. The mean volume of distribution after intravenous administration of Victoza is 0.07 L/kg. Liraglutide is extensively bound to plasma protein (>98%).

Metabolism - During the initial 24 hours following administration of a single [3 H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination.

Elimination - Following a [3 H]-liraglutide dose, intact liraglutide was not detected in urine or feces. Only a minor part of the administered radioactivity was excreted as liraglutide-

related metabolites in urine or feces (6% and 5%, respectively). The majority of urine and feces radioactivity was excreted during the first 6-8 days. The mean apparent clearance following subcutaneous administration of a single dose of liraglutide is approximately 1.2 L/h with an elimination half-life of approximately 13 hours, making Victoza suitable for once daily administration.

Specific Populations

Elderly - Age had no effect on the pharmacokinetics of Victoza based on a pharmacokinetic study in healthy elderly subjects (65 to 83 years) and population pharmacokinetic analyses of patients 18 to 80 years of age [see *Use in Specific Populations* (8.5)].

Gender - Based on the results of population pharmacokinetic analyses, females have 34% lower weight-adjusted clearance of Victoza compared to males. Based on the exposure response data, no dose adjustment is necessary based on gender.

Race and Ethnicity - Race and ethnicity had no effect on the pharmacokinetics of Victoza based on the results of population pharmacokinetic analyses that included Caucasian, Black, Asian and Hispanic/Non-Hispanic subjects.

Body Weight - Body weight significantly affects the pharmacokinetics of Victoza based on results of population pharmacokinetic analyses. The exposure of liraglutide decreases with an increase in baseline body weight. However, the 1.2 mg and 1.8 mg daily doses of Victoza provided adequate systemic exposures over the body weight range of 40 – 160 kg evaluated in the clinical trials. Liraglutide was not studied in patients with body weight >160 kg.

Pediatric - Victoza has not been studied in pediatric patients [see *Use in Specific Populations* (8.4)].

Renal Impairment - The single-dose pharmacokinetics of Victoza were evaluated in subjects with varying degrees of renal impairment. Subjects with mild (estimated creatinine clearance 50-80 mL/min) to severe (estimated creatinine clearance <30 mL/min) renal impairment and subjects with end-stage renal disease requiring dialysis were included in the trial. Compared to healthy subjects, liraglutide AUC in mild, moderate, and severe renal impairment and in end-stage renal disease was on average 35%, 19%, 29% and 30% lower, respectively [see *Use in Specific Populations* (8.6)].

Hepatic Impairment - The single-dose pharmacokinetics of Victoza were evaluated in subjects with varying degrees of hepatic impairment. Subjects with mild (Child Pugh score 5-6) to severe (Child Pugh score > 9) hepatic impairment were included in the trial. Compared to healthy subjects, liraglutide AUC in subjects with mild, moderate and severe hepatic impairment was on average 11%, 14% and 42% lower, respectively [see *Use in Specific Populations* (8.7)].

Drug Interactions

In vitro assessment of drug-drug interactions

Victoza has low potential for pharmacokinetic drug-drug interactions related to cytochrome P450 (CYP) and plasma protein binding.

In vivo assessment of drug-drug interactions

The drug-drug interaction studies were performed at steady state with Victoza 1.8 mg/day. Before administration of concomitant treatment, subjects underwent a 0.6 mg weekly dose increase to reach the maximum dose of 1.8 mg/day. Administration of the interacting drugs was timed so that C_{max} of Victoza (8-12 h) would coincide with the absorption peak of the co-administered drugs.

Digoxin

A single dose of digoxin 1 mg was administered 7 hours after the dose of Victoza at steady state. The concomitant administration with Victoza resulted in a reduction of digoxin AUC by 16%; C_{max} decreased by 31%. Digoxin median time to maximal concentration (T_{max}) was delayed from 1 h to 1.5 h.

Lisinopril

A single dose of lisinopril 20 mg was administered 5 minutes after the dose of Victoza at steady state. The co-administration with Victoza resulted in a reduction of lisinopril AUC by 15%; C_{max} decreased by 27%. Lisinopril median T_{max} was delayed from 6 h to 8 h with Victoza.

Atorvastatin

Victoza did not change the overall exposure (AUC) of atorvastatin following a single dose of atorvastatin 40 mg, administered 5 hours after the dose of Victoza at steady state. Atorvastatin C_{max} was decreased by 38% and median T_{max} was delayed from 1 h to 3 h with Victoza.

Acetaminophen

Victoza did not change the overall exposure (AUC) of acetaminophen following a single dose of acetaminophen 1000 mg, administered 8 hours after the dose of Victoza at steady state. Acetaminophen C_{max} was decreased by 31% and median T_{max} was delayed up to 15 minutes.

Griseofulvin

Victoza did not change the overall exposure (AUC) of griseofulvin following co-administration of a single dose of griseofulvin 500 mg with Victoza at steady state. Griseofulvin C_{max} increased by 37% while median T_{max} did not change.

Oral Contraceptives

A single dose of an oral contraceptive combination product containing 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel was administered under fed conditions and 7 hours after the dose of Victoza at steady state. Victoza lowered ethinylestradiol and levonorgestrel C_{max} by 12% and 13%, respectively. There was no effect of Victoza on the overall exposure (AUC) of ethinylestradiol. Victoza increased the levonorgestrel $AUC_{0-\infty}$ by 18%. Victoza delayed T_{max} for both ethinylestradiol and levonorgestrel by 1.5 h.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week carcinogenicity study was conducted in male and female CD-1 mice at doses of 0.03, 0.2, 1.0, and 3.0 mg/kg/day liraglutide administered by bolus subcutaneous injection yielding systemic exposures 0.2-, 2-, 10- and 45-times the human exposure, respectively, at the MRHD of 1.8 mg/day based on plasma AUC comparison. A dose-related increase in benign thyroid C-cell adenomas was seen in the 1.0 and the 3.0

mg/kg/day groups with incidences of 13% and 19% in males and 6% and 20% in females, respectively. C-cell adenomas did not occur in control groups or 0.03 and 0.2 mg/kg/day groups. Treatment-related malignant C-cell carcinomas occurred in 3% of females in the 3.0 mg/kg/day group. Thyroid C-cell tumors are rare findings during carcinogenicity testing in mice. A treatment-related increase in fibrosarcomas was seen on the dorsal skin and subcutis, the body surface used for drug injection, in males in the 3 mg/kg/day group. These fibrosarcomas were attributed to the high local concentration of drug near the injection site. The liraglutide concentration in the clinical formulation (6 mg/mL) is 10-times higher than the concentration in the formulation used to administer 3 mg/kg/day liraglutide to mice in the carcinogenicity study (0.6 mg/mL).

A 104-week carcinogenicity study was conducted in male and female Sprague Dawley rats at doses of 0.075, 0.25 and 0.75 mg/kg/day liraglutide administered by bolus subcutaneous injection with exposures 0.5-, 2- and 8-times the human exposure, respectively, resulting from the MRHD based on plasma AUC comparison. A treatment-related increase in benign thyroid C-cell adenomas was seen in males in 0.25 and 0.75 mg/kg/day liraglutide groups with incidences of 12%, 16%, 42%, and 46% and in all female liraglutide-treated groups with incidences of 10%, 27%, 33%, and 56% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. A treatment-related increase in malignant thyroid C-cell carcinomas was observed in all male liraglutide-treated groups with incidences of 2%, 8%, 6%, and 14% and in females at 0.25 and 0.75 mg/kg/day with incidences of 0%, 0%, 4%, and 6% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. Thyroid C-cell carcinomas are rare findings during carcinogenicity testing in rats.

Human relevance of thyroid C-cell tumors in mice and rats is unknown and could not be determined by clinical studies or nonclinical studies [see *Boxed Warning and Warnings and Precautions (5.1)*].

Liraglutide was negative with and without metabolic activation in the Ames test for mutagenicity and in a human peripheral blood lymphocyte chromosome aberration test for clastogenicity. Liraglutide was negative in repeat-dose *in vivo* micronucleus tests in rats.

In rat fertility studies using subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide, males were treated for 4 weeks prior to and throughout mating and females were treated 2 weeks prior to and throughout mating until gestation day 17. No direct adverse effects on male fertility was observed at doses up to 1.0 mg/kg/day, a high dose yielding an estimated systemic exposure 11- times the human exposure at the MRHD, based on plasma AUC. In female rats, an increase in early embryonic deaths occurred at 1.0 mg/kg/day. Reduced body weight gain and food consumption were observed in females at the 1.0 mg/kg/day dose.

14 CLINICAL STUDIES

A total of 4445 patients with type 2 diabetes participated in 6 phase 3 trials. There were 5 double-blind (one of these trials had an open-label active control insulin glargine arm), randomized, controlled clinical trials, one of 52 weeks duration and four of 26 weeks duration. There was also a 26 week open-label trial comparing Victoza to twice-daily exenatide. These multinational trials were conducted to evaluate the glycemic efficacy and safety of Victoza in type 2 diabetes as monotherapy and in combination with one or two oral anti-diabetic medications. The 5 add-on combination therapy trials enrolled

patients who were previously treated with anti-diabetic therapy, and approximately two-thirds of patients in the monotherapy trial also were previously treated with anti-diabetic therapy. In total, 272 (6%) of the 4445 patients in these 6 trials were new to anti-diabetic therapy. In these 6 clinical trials, patients ranged in age from 19-80 years old and 54% were men. Approximately 79% of patients were Caucasian, and 6% were Black. In the 3 trials where ethnicity was captured, 23% of patients were Hispanic/Latino (n=399). In each of these trials, treatment with Victoza produced clinically and statistically significant improvements in hemoglobin A_{1c} and fasting plasma glucose (FPG) compared to placebo. Victoza did not have adverse effects on blood pressure.

All Victoza-treated patients started at 0.6 mg/day. The dose was increased in weekly intervals by 0.6 mg to reach 1.2 mg or 1.8 mg for patients randomized to these higher doses. Victoza 0.6 mg is not effective for glycemic control and is intended only as a starting dose to reduce gastrointestinal intolerance [see *Dosage and Administration (2)*].

14.1 Monotherapy

In this 52-week trial, 746 patients were randomized to Victoza 1.2 mg, Victoza 1.8 mg, or glimepiride 8 mg. Patients who were randomized to glimepiride were initially treated with 2 mg daily for two weeks, increasing to 4 mg daily for another two weeks, and finally increasing to 8 mg daily. Treatment with Victoza 1.8 mg and 1.2 mg resulted in a statistically significant reduction in HbA_{1c} compared to glimepiride (Table 5). The percentage of patients who discontinued due to ineffective therapy was 3.6% in the Victoza 1.8 mg treatment group, 6.0% in the Victoza 1.2 mg treatment group, and 10.1% in the glimepiride-treatment group.

Table 5 Results of a 52-week monotherapy trial^a

	Victoza 1.8 mg	Victoza 1.2 mg	Glimepiride 8 mg
Intent-to-Treat Population (N)	246	251	248
HbA_{1c} (%) (Mean)			
Baseline	8.2	8.2	8.2
Change from baseline (adjusted mean) ^b	-1.1	-0.8	-0.5
Difference from glimepiride arm (adjusted mean) ^b			
95% Confidence Interval			
	-0.6**		
		(-0.8, -0.4)	-0.3*
		(-0.5, -0.1)	
Percentage of patients achieving A _{1c} <7%	51	43	28
Fasting Plasma Glucose (mg/dL) (Mean)			
Baseline	172	168	172
Change from baseline (adjusted mean) ^b	-26	-15	-5
Difference from glimepiride arm (adjusted mean) ^b			
95% Confidence Interval			
	-20**		

(-29, -12)

-10*

(-19, -1)

Body Weight (kg) (Mean)

Baseline	92.6	92.1	93.3
Change from baseline (adjusted mean) ^b	-2.5	-2.1	+1.1
Difference from glimepiride arm (adjusted mean) ^b			

95% Confidence Interval
-3.6**

(-4.3, -2.9) -3.2**

(-3.9, -2.5)

^aIntent-to-treat population using last observation on study

^bLeast squares mean adjusted for baseline value

*p-value <0.05

**p-value <0.0001

<< OLE Object: Picture (Enhanced Metafile) >>

Figure 3 Mean HbA_{1c} for patients who completed the 52-week trial and for the Last Observation Carried Forward (LOCF, intent-to-treat) data at Week 52 (Monotherapy)

14.2 Combination Therapy

Add-on to Metformin

In this 26-week trial, 1091 patients were randomized to Victoza 0.6 mg, Victoza 1.2 mg, Victoza 1.8 mg, placebo, or glimepiride 4 mg (one-half of the maximal approved dose in the United States), all as add-on to metformin. Randomization occurred after a 6-week run-in period consisting of a 3-week initial forced metformin titration period followed by a maintenance period of another 3 weeks. During the titration period, doses of metformin were increased up to 2000 mg/day.

Treatment with Victoza 1.2 mg and 1.8 mg as add-on to metformin resulted in a significant mean HbA_{1c} reduction relative to placebo add-on to metformin and resulted in a similar mean HbA_{1c} reduction relative to glimepiride 4 mg add-on to metformin (Table 6). The percentage of patients who discontinued due to ineffective therapy was 5.4% in the Victoza 1.8 mg + metformin treatment group, 3.3% in the Victoza 1.2 mg + metformin treatment group, 23.8% in the placebo + metformin treatment group, and 3.7% in the glimepiride + metformin treated group.

Table 6 Results of a 26-week trial of Victoza as add-on to metformin^a

Victoza 1.8 mg +

Metformin Victoza 1.2 mg +

Metformin Placebo +

Metformin Glimepiride 4 mg[†] +

Metformin

Intent-to-Treat Population (N) 242 240 121 242

HbA_{1c} (%) (Mean)

Baseline 8.4 8.3 8.4 8.4

Change from baseline (adjusted mean)^b -1.0 -1.0 +0.1 -1.0

Difference from placebo + metformin arm (adjusted mean)^b

95% Confidence Interval

-1.1**

(-1.3, -0.9) -1.1**

(-1.3, -0.9)

Difference from glimepiride + metformin arm (adjusted mean)^b

95% Confidence Interval

0.0

(-0.2, 0.2) 0.0

(-0.2, 0.2)

Percentage of patients achieving A_{1c} <7% 42 35 11 36

Fasting Plasma Glucose (mg/dL) (Mean)

Baseline 181 179 182 180

Change from baseline (adjusted mean)^b -30 -30 +7 -24

Difference from placebo + metformin arm (adjusted mean)^b

95% Confidence Interval -38**

(-48, -27) -37**

(-47, -26)

Difference from glimepiride + metformin arm (adjusted mean)^b

95% Confidence Interval

-7

(-16, 2) -6

(-15, 3)

Body Weight (kg) (Mean)

Baseline 88.0 88.5 91.0 89.0

Change from baseline (adjusted mean)^b -2.8 -2.6 -1.5 +1.0

Difference from placebo + metformin arm (adjusted mean)^b

95% Confidence Interval
-1.3*

(-2.2, -0.4) -1.1*

(-2.0, -0.2)
Difference from glimepiride + metformin arm (adjusted mean)^b

95% Confidence Interval
-3.8**

(-4.5, -3.0) -3.5**

(-4.3, -2.8)

^aIntent-to-treat population using last observation on study

^bLeast squares mean adjusted for baseline value

[†] For glimepiride, one-half of the maximal approved United States dose.

*p-value <0.05

**p-value <0.0001

Add-on to Sulfonylurea

In this 26-week trial, 1041 patients were randomized to Victoza 0.6 mg, Victoza 1.2 mg, Victoza 1.8 mg, placebo, or rosiglitazone 4 mg (one-half of the maximal approved dose in the United States), all as add-on to glimepiride. Randomization occurred after a 4-week run-in period consisting of an initial, 2-week, forced-glimepiride titration period followed by a maintenance period of another 2 weeks. During the titration period, doses of glimepiride were increased to 4 mg/day. The doses of glimepiride could be reduced (at the discretion of the investigator) from 4 mg/day to 3 mg/day or 2 mg/day (minimum) after randomization, in the event of unacceptable hypoglycemia or other adverse events.

Treatment with Victoza 1.2 mg and 1.8 mg as add-on to glimepiride resulted in a statistically significant reduction in mean HbA_{1c} compared to placebo add-on to glimepiride (Table 7). The percentage of patients who discontinued due to ineffective therapy was 3.0% in the Victoza 1.8 mg + glimepiride treatment group, 3.5% in the Victoza 1.2 mg + glimepiride treatment group, 17.5% in the placebo + glimepiride treatment group, and 6.9% in the rosiglitazone + glimepiride treatment group.

Table 7 Results of a 26-week trial of Victoza as add-on to sulfonylurea^a

Victoza 1.8 mg +
Glimepiride Victoza 1.2 mg +
Glimepiride Placebo +

Glimepiride Rosiglitazone 4 mg[†] +

Glimepiride				
Intent-to-Treat Population (N)	234	228	114	231
HbA_{1c} (%) (Mean)				
Baseline	8.5	8.5	8.4	8.4
Change from baseline (adjusted mean) ^b	-1.1	-1.1	+0.2	-0.4
Difference from placebo + glimepiride arm (adjusted mean) ^b				

95% Confidence Interval
-1.4**

(-1.6, -1.1) -1.3**

Glimepiride				
Percentage of patients achieving A_{1c} <7%	42	35	7	22

Fasting Plasma Glucose (mg/dL) (Mean)				
Baseline	174	177	171	179
Change from baseline (adjusted mean) ^b	-29	-28	+18	-16
Difference from placebo + glimepiride arm (adjusted mean) ^b				

95% Confidence Interval -47**

(-58, -35) -46**

Body Weight (kg) (Mean)				
Baseline	83.0	80.0	81.9	80.6
Change from baseline (adjusted mean) ^b	-0.2	+0.3	-0.1	+2.1
Difference from placebo + glimepiride arm (adjusted mean) ^b				

95% Confidence Interval
-0.1

(-0.9, 0.6) 0.4

(-0.4, 1.2)

^aIntent-to-treat population using last observation on study

^bLeast squares mean adjusted for baseline value

[†] For rosiglitazone, one-half of the maximal approved United States dose.

**p-value <0.0001

Add-on to Metformin and Sulfonylurea

In this 26-week trial, 581 patients were randomized to Victoza 1.8 mg, placebo, or insulin glargine, all as add-on to metformin and glimepiride. Randomization took place after a 6-week run-in period consisting of a 3-week forced metformin and glimepiride titration period followed by a maintenance period of another 3 weeks. During the titration period, doses of metformin and glimepiride were to be increased up to 2000 mg/day and 4 mg/day, respectively. After randomization, patients randomized to Victoza

1.8 mg underwent a 2 week period of titration with Victoza. During the trial, the Victoza and metformin doses were fixed, although glimepiride and insulin glargine doses could be adjusted. Patients titrated glargine twice-weekly during the first 8 weeks of treatment based on self-measured fasting plasma glucose on the day of titration. After Week 8, the frequency of insulin glargine titration was left to the discretion of the investigator, but, at a minimum, the glargine dose was to be revised, if necessary, at Weeks 12 and 18. Only 20% of glargine-treated patients achieved the pre-specified target fasting plasma glucose of ≤ 100 mg/dL. Therefore, optimal titration of the insulin glargine dose was not achieved in most patients.

Treatment with Victoza as add-on to glimepiride and metformin resulted in a statistically significant mean reduction in HbA_{1c} compared to placebo add-on to glimepiride and metformin (Table 8). The percentage of patients who discontinued due to ineffective therapy was 0.9% in the Victoza 1.8 mg + metformin + glimepiride treatment group, 0.4% in the insulin glargine + metformin + glimepiride treatment group, and 11.3% in the placebo + metformin + glimepiride treatment group.

Table 8 Results of a 26-week trial of Victoza as add-on to metformin and sulfonylurea^a

	Victoza 1.8 mg +		
	Metformin +		
	Glimepiride	Placebo +	
	Metformin +		
	Glimepiride	Insulin glargine[†] +	
	Metformin +		
	Glimepiride		
Intent-to-Treat Population (N)	230	114	232
HbA_{1c} (%) (Mean)			
Baseline	8.3	8.3	8.1
Change from baseline (adjusted mean) ^b		-1.3	-0.2
Difference from placebo + metformin + glimepiride arm (adjusted mean) ^b			-1.1

95% Confidence Interval
-1.1**

	(-1.3, -0.9)		
Percentage of patients achieving A _{1c} <7%	53	15	46
Fasting Plasma Glucose (mg/dL) (Mean)			
Baseline	165	170	164
Change from baseline (adjusted mean) ^b		-28	+10
Difference from placebo + metformin + glimepiride arm (adjusted mean) ^b			-32

95% Confidence Interval

-38**

(-46, -30)

Body Weight (kg) (Mean)

Baseline 85.8 85.4 85.2

Change from baseline (adjusted mean)^b -1.8 -0.4 1.6

Difference from placebo + metformin + glimepiride arm (adjusted mean)^b

95% Confidence Interval

-1.4*

(-2.1, -0.7)

^aIntent-to-treat population using last observation on study

^bLeast squares mean adjusted for baseline value

[†] For insulin glargine, optimal titration regimen was not achieved for 80% of patients.

*p-value <0.05

**p-value <0.0001

Victoza versus Exenatide, Both as Add-on to Metformin and/or Sulfonylurea Therapy

In this 26-week, open-label trial, 464 patients on a background of metformin monotherapy, sulfonylurea monotherapy or a combination of metformin and sulfonylurea were randomized to once daily Victoza 1.8 mg or exenatide 10 mcg twice daily. Maximally tolerated doses of background therapy were to remain unchanged for the duration of the trial. Patients randomized to exenatide started on a dose of 5 mcg twice-daily for 4 weeks and then were escalated to 10 mcg twice daily.

Treatment with Victoza 1.8 mg resulted in statistically significant reductions in HbA_{1c} and FPG relative to exenatide (Table 9). The percentage of patients who discontinued for ineffective therapy was 0.4% in the Victoza treatment group and 0% in the exenatide treatment group. Both treatment groups had a mean decrease from baseline in body weight of approximately 3 kg.

Table 9 Results of a 26-week open-label trial of Victoza versus Exenatide (both in combination with metformin and/or sulfonylurea)^a

Victoza

1.8 mg once daily

+ metformin and/or sulfonylurea Exenatide

10 mcg twice daily

+ metformin and/or sulfonylurea

Intent-to-Treat Population (N) 233 231

HbA_{1c} (%) (Mean)

	Baseline	8.2	8.1	
Change from baseline (adjusted mean) ^b				-1.1
Difference from exenatide arm (adjusted mean) ^b				-0.8

95% Confidence Interval
-0.3**

		(-0.5, -0.2)		
Percentage of patients achieving A _{1c} <7%			54	43
Fasting Plasma Glucose (mg/dL) (Mean)				
Baseline	176	171		
Change from baseline (adjusted mean) ^b			-29	-11
Difference from exenatide arm (adjusted mean) ^b				

95% Confidence Interval
-18**

(-25, -12)
^aIntent-to-treat population using last observation carried forward

^bLeast squares mean adjusted for baseline value
**p-value <0.0001

Add-on to Metformin and Thiazolidinedione

In this 26-week trial, 533 patients were randomized to Victoza 1.2 mg, Victoza 1.8 mg or placebo, all as add-on to rosiglitazone (8 mg) plus metformin (2000 mg). Patients underwent a 9 week run-in period (3- week forced dose escalation followed by a 6-week dose maintenance phase) with rosiglitazone (starting at 4 mg and increasing to 8 mg/day within 2 weeks) and metformin (starting at 500 mg with increasing weekly increments of 500 mg to a final dose of 2000 mg/day). Only patients who tolerated the final dose of rosiglitazone (8 mg/day) and metformin (2000 mg/day) and completed the 6-week dose maintenance phase were eligible for randomization into the trial.

Treatment with Victoza as add-on to metformin and rosiglitazone produced a statistically significant reduction in mean HbA_{1c} compared to placebo add-on to metformin and rosiglitazone (Table 10). The percentage of patients who discontinued due to ineffective therapy was 1.7% in the Victoza 1.8 mg + metformin + rosiglitazone treatment group, 1.7% in the Victoza 1.2 mg + metformin + rosiglitazone treatment group, and 16.4% in the placebo + metformin + rosiglitazone treatment group.

Table 10 Results of a 26-week trial of Victoza as add-on to metformin and thiazolidinedione^a

Victoza 1.8 mg +
Metformin +
Rosiglitazone Victoza 1.2 mg +

Metformin +

Rosiglitazone Placebo + Metformin +

Rosiglitazone

Intent-to-Treat Population (N) 178 177 175

HbA_{1c} (%) (Mean)

Baseline 8.6 8.5 8.4

Change from baseline (adjusted mean)^b -1.5 -1.5 -0.5

Difference from placebo + metformin + rosiglitazone arm (adjusted mean)^b

95% Confidence Interval

-0.9**

(-1.1, -0.8) -0.9**

(-1.1, -0.8)

Percentage of patients achieving A_{1c} <7% 54 57 28

Fasting Plasma Glucose (mg/dL) (Mean)

Baseline 185 181 179

Change from baseline (adjusted mean)^b -44 -40 -8

Difference from placebo + metformin + rosiglitazone arm (adjusted mean)^b

95% Confidence Interval

-36**

(-44, -27) -32**

(-41, -23)

Body Weight (kg) (Mean)

Baseline 94.9 95.3 98.5

Change from baseline (adjusted mean)^b -2.0 -1.0 +0.6

Difference from placebo + metformin + rosiglitazone arm (adjusted mean)^b

95% Confidence Interval

-2.6**

(-3.4, -1.8) -1.6**

(-2.4, -1.0)

^aIntent-to-treat population using last observation on study

^bLeast squares mean adjusted for baseline value

**p-value <0.0001

16 HOW SUPPLIED/STORAGE HANDLING

16.1 How Supplied

Victoza is available in the following package sizes containing disposable, pre-filled, multi-dose pens. Each individual pen delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg (6 mg/mL, 3

mL).

2 x Victoza pen NDC 0169-4060-12
3 x Victoza pen NDC 0169-4060-13

Each Victoza pen is for use by a single patient. A Victoza pen should never be shared between patients, even if the needle is changed.

16.2 Recommended Storage

Prior to first use, Victoza should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C) (Table 11). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze Victoza and do not use Victoza if it has been frozen.

After initial use of the Victoza pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use. Victoza should be protected from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the Victoza pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy.

Table 11 Recommended Storage Conditions for the Victoza Pen

Prior to first use	After first use
	Refrigerated 36°F to 46°F
(2°C to 8°C)	Room Temperature 59°F to 86°F
(15°C to 30°C)	Refrigerated 36°F to 46°F
	(2°C to 8°C) Until expiration date 30 days

17 PATIENT COUNSELING INFORMATION

17.1 Risk of Thyroid C-cell Tumors

Patients should be informed that liraglutide causes benign and malignant thyroid C-cell tumors in mice and rats and that the human relevance of this finding is unknown. Patients should be counseled to report symptoms of thyroid tumors (e.g., a lump in the neck, hoarseness, dysphagia or dyspnea) to their physician.

17.2 Dehydration and Renal Failure

Patients treated with Victoza should be advised of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. Patients should be informed of the potential risk for worsening renal function, which in some cases may require dialysis.

17.3 Pancreatitis

Patients should be informed that persistent severe abdominal pain, that may radiate to the back and which may (or may not) be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Patients should be instructed to discontinue Victoza promptly, and to contact their physician, if persistent severe abdominal pain occurs [see *Warnings and Precautions (5.2)*].

17.4 Never Share a Victoza Pen Between Patients

Counsel patients that they should never share a Victoza pen with another person, even if the needle is changed. Sharing of the pen between patients may pose a risk of transmission of infection.

17.5 Instructions

Patients should be informed of the potential risks and benefits of Victoza and of alternative modes of therapy. Patients should also be informed about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A_{1c} testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be advised to seek medical advice promptly.

Patients should be advised that the most common side effects of Victoza are headache, nausea and diarrhea. Nausea is most common when first starting Victoza, but decreases over time in the majority of patients and does not typically require discontinuation of Victoza.

Physicians should instruct their patients to read the Patient Medication Guide before starting Victoza therapy and to reread each time the prescription is renewed. Patients should be instructed to inform their doctor or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

17.6 Laboratory Tests

Patients should be informed that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and A_{1c} levels, with a goal of decreasing these levels towards the normal range. A_{1c} is especially useful for evaluating long-term glycemic control.

17.7 FDA-Approved Medication Guide

See separate leaflet.

Date of Issue: May 18, 2011

Version: 3

Victoza[®] is a registered trademark of Novo Nordisk A/S.

Victoza[®] is covered by US Patent Nos. 6,268,343, 6,458,924 and 7,235,627 and other patents pending.

Victoza® Pen is covered by US Patent Nos. 6,004,297, 6,235,004, 6,582,404 and other patents pending.

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Highlights of Prescribing Information

These highlights do not include all the information needed to use Norditropin Cartridges safely and effectively. See full prescribing information for Norditropin Cartridges.

Norditropin® Cartridges [somatropin (rDNA origin) injection], for subcutaneous use

Initial U.S. Approval: 1987

-----**RECENT MAJOR CHANGES**-----

- Warnings and Precautions, Pancreatitis (5.14) 12/2010
- Warnings and Precautions, Impaired Glucose Tolerance and Diabetes Mellitus (5.4) 3/2011

-----**INDICATIONS AND USAGE**-----

Norditropin is a recombinant human growth hormone indicated for:

- **Pediatric:** Treatment of children with growth failure due to growth hormone deficiency (GHD), short stature associated with Noonan syndrome, short stature associated with Turner syndrome and short stature born SGA with no catch-up growth by age 2 to 4 years (1.1)
- **Adult:** Treatment of adults with either adult onset or childhood onset GHD (1.2)

-----**DOSAGE AND ADMINISTRATION**-----

Norditropin should be administered subcutaneously (2).

- **Pediatric GHD:** 0.024 to 0.034 mg/kg/day, 6 to 7 times a week (2.1)
- **Noonan Syndrome:** Up to 0.066 mg/kg/day (2.1)

- **Turner Syndrome:** Up to 0.067 mg/kg/day (2.1)
- **SGA:** Up to 0.067 mg/kg/day (2.1)
- **Adult GHD:** 0.004 mg/kg/day to be increased as tolerated to not more than 0.016 mg/kg/day after approximately 6 weeks, or a starting dose of approximately 0.2 mg/day (range, 0.15 to 0.30 mg/day) increased gradually every 1 to 2 months by increments of approximately 0.1 to 0.2 mg/day (2.2)
- Norditropin cartridges must be used with their corresponding color-coded NordiPen delivery systems (2.3)
- Injection sites should always be rotated to avoid lipoatrophy (2.3)

.....**DOSAGE FORMS AND STRENGTHS**.....

Norditropin is preloaded in the Norditropin FlexPro or Norditropin NordiFlex pens, or cartridges for use with the corresponding NordiPens (3):

- 5 mg/1.5 mL (orange): FlexPro and NordiFlex pens, and cartridges
- 10 mg/1.5 mL (blue): FlexPro and NordiFlex pens
- 15 mg/1.5 mL (green): FlexPro and NordiFlex pens, and cartridges
- 30 mg/3 mL (purple): Norditropin NordiFlex pen only

.....**CONTRAINDICATIONS**.....

- Acute Critical Illness (4.1, 5.1)
- Children with Prader-Willi syndrome who are severely obese or have severe respiratory impairment – reports of sudden death (4.2, 5.2)
- Active Malignancy (4.3)
- Active Proliferative or Severe Non-Proliferative Diabetic Retinopathy (4.4)
- Children with closed epiphyses (4.5)
- Known hypersensitivity to somatotropin or excipients (4.6)

.....**WARNINGS AND PRECAUTIONS**.....

- Acute Critical Illness: Potential benefit of treatment continuation should be weighed against the potential risk (5.1)
- Prader-Willi Syndrome in Children: Evaluate for signs of upper airway obstruction and sleep apnea before initiation of treatment for GHD. Discontinue treatment if these signs occur (5.2)
- Neoplasm: Monitor patients with preexisting tumors for progression or recurrence. Increased risk of a second neoplasm in childhood cancer survivors treated with somatotropin - in particular meningiomas in patients treated with radiation to the head for their first neoplasm (5.3)
- Impaired Glucose Tolerance and Diabetes Mellitus: May be unmasked. Periodically monitor glucose levels in all patients. Doses of concurrent antihyperglycemic drugs in diabetics may require adjustment (5.4)
- Intracranial Hypertension: Exclude preexisting papilledema. May develop and is usually reversible after discontinuation or dose reduction (5.5)
- Fluid Retention (i.e., edema, arthralgia, carpal tunnel syndrome – especially in adults): May occur frequently. Reduce dose as necessary (5.6)
- Hypothyroidism: May first become evident or worsen (5.7)
- Slipped Capital Femoral Epiphysis: May develop. Evaluate children with the onset of a limp or hip/knee pain (5.8)

- Progression of Preexisting Scoliosis: May develop (5.9)
- Pancreatitis: Consider pancreatitis in patients with persistent severe abdominal pain. (5.14)

.....**ADVERSE REACTIONS**.....

Other common somatropin-related adverse reactions include injection site reactions/rashes and lipoatrophy (6.1) and headaches (6.3).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk at 1-888-NOVO-444 ([1-888-668-6444](tel:1-888-668-6444)) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

.....**DRUG INTERACTIONS**.....

- Inhibition of 11 β -Hydroxysteroid Dehydrogenase Type 1: May require the initiation of glucocorticoid replacement therapy. Patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance doses (7.1)
- Glucocorticoid Replacement: Should be carefully adjusted (7.2)
- Cytochrome P450-Metabolized Drugs: Monitor carefully if used with somatropin (7.3)
- Oral Estrogen: Larger doses of somatropin may be required in women (7.4)
- Insulin and/or Oral/Injectable Hypoglycemic Agents: May require adjustment (7.5)

See 17 for PATIENT COUNSELING INFORMATION
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*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1 Pediatric Patients

Norditropin [somatropin (rDNA origin) injection] is indicated for the treatment of pediatric patients with growth failure due to inadequate secretion of endogenous growth hormone (GH).

Norditropin [somatropin (rDNA origin) injection] is indicated for the treatment of pediatric patients with short stature associated with Noonan syndrome.

Norditropin [somatropin (rDNA origin) injection] is indicated for the treatment of pediatric patients with short stature associated with Turner syndrome.

Norditropin [somatropin (rDNA origin) injection] is indicated for the treatment of pediatric patients with short stature born small for gestational age (SGA) with no catch-up growth by age 2 to 4 years.

1.2 Adult Patients

Norditropin [somatropin (rDNA origin) injection] is indicated for the replacement of endogenous GH in adults with growth hormone deficiency (GHD) who meet either of the following two criteria:

- Adult Onset (AO): Patients who have GHD, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or
- Childhood Onset (CO): Patients who were GH deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

Patients who were treated with somatropin for GHD in childhood and whose epiphyses are closed should be reevaluated before continuation of somatropin therapy at the reduced dose level recommended for GHD adults. According to current standards, confirmation of the diagnosis of adult GHD in both groups involves an appropriate growth hormone provocative test with two exceptions: (1) patients with multiple other pituitary

hormone deficiencies due to organic disease; and (2) patients with congenital/genetic growth hormone deficiency.

2 DOSAGE AND ADMINISTRATION

For subcutaneous injection.

Therapy with Norditropin should be supervised by a physician who is experienced in the diagnosis and management of pediatric patients with short stature associated with GHD, Noonan syndrome, Turner syndrome or SGA, and adult patients with either childhood onset or adult onset GHD.

2.1 Dosing of Pediatric Patients

General Pediatric Dosing Information

The Norditropin dosage and administration schedule should be individualized based on the growth response of each patient. Serum insulin-like growth factor I (IGF-I) levels may be useful during dose titration.

Response to somatropin therapy in pediatric patients tends to decrease with time. However, in pediatric patients, the failure to increase growth rate, particularly during the first year of therapy, indicates the need for close assessment of compliance and evaluation for other causes of growth failure, such as hypothyroidism, undernutrition, advanced bone age and antibodies to recombinant human GH (rhGH).

Treatment with Norditropin for short stature should be discontinued when the epiphyses are fused.

Pediatric Growth Hormone Deficiency (GHD)

A dosage of 0.024 to 0.034 mg/kg/day, 6 to 7 times a week, is recommended.

Pediatric Patients with Short Stature Associated with Noonan Syndrome

Not all patients with Noonan syndrome have short stature; some will achieve a normal adult height without treatment. Therefore, prior to initiating Norditropin for a patient with Noonan syndrome, establish that the patient does have short stature.

A dosage of up to 0.066 mg/kg/day is recommended.

Pediatric Patients with Short Stature Associated with Turner Syndrome

A dosage of up to 0.067 mg/kg/day is recommended.

Pediatric Patients with Short Stature Born Small for Gestational Age (SGA) with No Catch-up Growth by Age 2 to 4 Years

A dosage of up to 0.067 mg/kg/day is recommended.

Recent literature has recommended initial treatment with larger doses of somatropin (e.g., 0.067 mg/kg/day), especially in very short children (i.e., HSDS < -3), and/or older/pubertal children, and that a reduction in dosage (e.g., gradually towards 0.033 mg/kg/day) should be considered if substantial catch-up growth is observed during the first few years of therapy. On the other hand, in younger SGA children (e.g., approximately < 4 years) (who respond the best in general) with less severe short stature (i.e., baseline HSDS values between -2 and -3), consideration should be given to initiating treatment at a lower dose (e.g., 0.033 mg/kg/day), and titrating the dose as

needed over time. In all children, clinicians should carefully monitor the growth response, and adjust the rhGH dose as necessary.

2.2 Dosing of Adult Patients

Adult Growth Hormone Deficiency (GHD)

Either of two approaches to Norditropin dosing may be followed: a non-weight-based regimen or a weight-based regimen.

Non-weight based — based on published consensus guidelines, a starting dose of approximately 0.2 mg/day (range, 0.15-0.30 mg/day) may be used without consideration of body weight. This dose can be increased gradually every 1 to 2 months by increments of approximately 0.1-0.2 mg/day, according to individual patient requirements based on the clinical response and serum insulin-like growth factor I (IGF-I) concentrations. The dose should be decreased as necessary on the basis of adverse events and/or serum IGFI concentrations above the age- and gender-specific normal range. Maintenance dosages vary considerably from person to person, and between male and female patients.

Weight-based — based on the dosing regimen used in the original adult GHD registration trials, the recommended dosage at the start of treatment is not more than 0.004 mg/kg/day. The dose may be increased to not more than 0.016 mg/kg/day after approximately 6 weeks according to individual patient requirements. Clinical response, side effects, and determination of age- and gender-adjusted serum IGF-I concentrations should be used as guidance in dose titration.

A lower starting dose and smaller dose increments should be considered for older patients, who are more prone to the adverse effects of somatropin than younger individuals. In addition, obese individuals are more likely to manifest adverse effects when treated with a weight-based regimen. In order to reach the defined treatment goal, estrogen-replete women may need higher doses than men. Oral estrogen administration may increase the dose requirements in women.

2.3 Preparation and Administration

Norditropin® FlexPro® 5 mg/1.5 mL, 10 mg/1.5 mL and 15 mg/1.5 mL:

Instructions for delivering the dosage are provided in the PATIENT INFORMATION and INSTRUCTIONS FOR USE leaflets enclosed with the Norditropin FlexPro prefilled pen.

Norditropin NordiFlex® 5 mg/1.5 mL, 10 mg/1.5 mL, 15 mg/1.5 mL and 30 mg/3 mL:

Instructions for delivering the dosage are provided in the PATIENT INFORMATION and INSTRUCTIONS FOR USE leaflets enclosed with the Norditropin NordiFlex prefilled pen.

Norditropin Cartridges must be administered using the NordiPen delivery systems. Each cartridge size has a corresponding, color-coded pen which is graduated to deliver the appropriate dose based on the concentration of Norditropin in the cartridge.

Norditropin® Cartridges 5 mg/1.5 mL and 15 mg/1.5 mL:

Each cartridge of Norditropin must be inserted into its corresponding NordiPen delivery system. Instructions for delivering the dosage are provided in the NordiPen INSTRUCTION booklet.

Parenteral drug products should always be inspected visually for particulate matter and

discoloration prior to administration, whenever solution and container permit. Norditropin MUST NOT BE INJECTED if the solution is cloudy or contains particulate matter. Use it only if it is clear and colorless.

Injection sites should always be rotated to avoid lipoatrophy.

3 DOSAGE FORMS AND STRENGTHS

Norditropin is available preloaded in the Norditropin FlexPro or Norditropin NordiFlex pens or in cartridges for use with the corresponding NordiPens:

- 5 mg/1.5 mL (orange): Norditropin FlexPro and Norditropin NordiFlex prefilled pens, and cartridges
- 10 mg/1.5 mL (blue): Norditropin FlexPro and Norditropin NordiFlex prefilled pens
- 15 mg/1.5 mL (green): Norditropin FlexPro and Norditropin NordiFlex prefilled pens, and cartridges
- 30 mg/3 mL (purple): Norditropin NordiFlex prefilled pen only

4 CONTRAINDICATIONS

4.1 Acute Critical Illness

Treatment with pharmacologic amounts of somatropin is contraindicated in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure. Two placebo-controlled clinical trials in non-growth hormone deficient adult patients (n=522) with these conditions in intensive care units revealed a significant increase in mortality (41.9% vs. 19.3%) among somatropin-treated patients (doses 5.3-8 mg/day) compared to those receiving placebo [*see Warnings and Precautions (5.1)*].

4.2 Prader-Willi Syndrome in Children

Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment [*see Warnings and Precautions (5.2)*]. There have been reports of sudden death when somatropin was used in such patients [*see Warnings and Precautions (5.2)*]. Norditropin is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

4.3 Active Malignancy

In general, somatropin is contraindicated in the presence of active malignancy. Any preexisting malignancy should be inactive and its treatment complete prior to instituting therapy with somatropin. Somatropin should be discontinued if there is evidence of recurrent activity. Since GHD may be an early sign of the presence of a pituitary tumor (or, rarely, other brain tumors), the presence of such tumors should be ruled out prior to initiation of treatment. Somatropin should not be used in patients with any evidence of progression or recurrence of an underlying intracranial tumor.

4.4 Diabetic Retinopathy

Somatropin is contraindicated in patients with active proliferative or severe non-proliferative diabetic retinopathy.

4.5 Closed Epiphyses

Somatropin should not be used for growth promotion in pediatric patients with closed epiphyses.

4.6 Hypersensitivity

Norditropin is contraindicated in patients with a known hypersensitivity to somatropin or

any of its excipients. Localized reactions are the most common hypersensitivity reactions.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Critical Illness

Increased mortality in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure has been reported after treatment with pharmacologic amounts of somatropin [see *Contraindications (4.1)*]. The safety of continuing somatropin treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation with somatropin in patients experiencing acute critical illnesses should be weighed against the potential risk.

5.2 Prader-Willi Syndrome in Children

There have been reports of fatalities after initiating therapy with somatropin in pediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnea, or unidentified respiratory infection. Male patients with one or more of these factors may be at greater risk than females. Patients with Prader-Willi syndrome should be evaluated for signs of upper airway obstruction and sleep apnea before initiation of treatment with somatropin. If, during treatment with somatropin, patients show signs of upper airway obstruction (including onset of or increased snoring) and/or new onset sleep apnea, treatment should be interrupted. All patients with Prader-Willi syndrome treated with somatropin should also have effective weight control and be monitored for signs of respiratory infection, which should be diagnosed as early as possible and treated aggressively [see *Contraindications (4.2)*]. Norditropin is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

5.3 Neoplasms

Patients with preexisting tumors or GHD secondary to an intracranial lesion should be monitored routinely for progression or recurrence of the underlying disease process. In pediatric patients, clinical literature has revealed no relationship between somatropin replacement therapy and central nervous system (CNS) tumor recurrence or new extracranial tumors. However, in childhood cancer survivors, an increased risk of a second neoplasm has been reported in patients treated with somatropin after their first neoplasm. Intracranial tumors, in particular meningiomas, in patients treated with radiation to the head for their first neoplasm, were the most common of these second neoplasms. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and CNS tumor recurrence.

Patients should be monitored carefully for potential malignant transformation of skin lesions, i.e. increased growth of preexisting nevi.

5.4 Impaired Glucose Tolerance and Diabetes Mellitus

Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses in susceptible patients. As a result, previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked during somatropin treatment. New onset type 2 Diabetes Mellitus has been reported in patients. Therefore, glucose levels should be monitored periodically in all patients treated with somatropin, especially in those with risk factors for diabetes mellitus, such as obesity, Turner syndrome, or a family history of diabetes mellitus. Patients with preexisting type 1 or type 2 diabetes mellitus or impaired

glucose tolerance should be monitored closely during somatropin therapy. The doses of antihyperglycemic drugs (i.e., insulin or oral/injectable agents) may require adjustment when somatropin therapy is instituted in these patients.

5.5 Intracranial Hypertension

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or vomiting has been reported in a small number of patients treated with somatropin products. Symptoms usually occurred within the first eight (8) weeks after the initiation of somatropin therapy. In all reported cases, IH-associated signs and symptoms rapidly resolved after cessation of therapy or a reduction of the somatropin dose.

Funduscopy examination should be performed routinely before initiating treatment with somatropin to exclude preexisting papilledema, and periodically during the course of somatropin therapy. If papilledema is observed by funduscopy during somatropin treatment, treatment should be stopped. If somatropin-induced IH is diagnosed, treatment with somatropin can be restarted at a lower dose after IH-associated signs and symptoms have resolved. Patients with Turner syndrome may be at increased risk for the development of IH.

5.6 Fluid Retention

Fluid retention during somatropin replacement therapy in adults may frequently occur. Clinical manifestations of fluid retention are usually transient and dose dependent.

5.7 Hypothyroidism

Undiagnosed/untreated hypothyroidism may prevent an optimal response to somatropin, in particular, the growth response in children. Patients with Turner syndrome have an inherently increased risk of developing autoimmune thyroid disease and primary hypothyroidism. In patients with GHD, central (secondary) hypothyroidism may first become evident or worsen during somatropin treatment. Therefore, patients treated with somatropin should have periodic thyroid function tests and thyroid hormone replacement therapy should be initiated or appropriately adjusted when indicated.

In patients with hypopituitarism (multiple hormone deficiencies), standard hormonal replacement therapy should be monitored closely when somatropin therapy is administered.

5.8 Slipped Capital Femoral Epiphysis in Pediatric Patients

Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders (including GHD and Turner syndrome) or in patients undergoing rapid growth. Any pediatric patient with the onset of a limp or complaints of hip or knee pain during somatropin therapy should be carefully evaluated.

5.9 Progression of Preexisting Scoliosis in Pediatric Patients

Progression of scoliosis can occur in patients who experience rapid growth. Because somatropin increases growth rate, patients with a history of scoliosis who are treated with somatropin should be monitored for progression of scoliosis. However, somatropin has not been shown to increase the occurrence of scoliosis. Skeletal abnormalities including scoliosis are commonly seen in untreated patients with Turner syndrome and Noonan syndrome. Scoliosis is also commonly seen in untreated patients with PraderWilli syndrome. Physicians should be alert to these abnormalities, which may manifest during

somatropin therapy.

5.10 Otitis Media and Cardiovascular Disorders in Turner Syndrome

Patients with Turner syndrome should be evaluated carefully for otitis media and other ear disorders since these patients have an increased risk of ear and hearing disorders. Somatropin treatment may increase the occurrence of otitis media in patients with Turner syndrome. In addition, patients with Turner syndrome should be monitored closely for cardiovascular disorders (e.g., stroke, aortic aneurysm/dissection, hypertension) as these patients are also at risk for these conditions.

5.11 Confirmation of Childhood Onset Adult GHD

Patients with epiphyseal closure who were treated with somatropin replacement therapy in childhood should be reevaluated according to the criteria in *Indications and Usage (1.2)* before continuation of somatropin therapy at the reduced dose level recommended for GH deficient adults.

5.12 Local and Systemic Reactions

When somatropin is administered subcutaneously at the same site over a long period of time, tissue atrophy may result. This can be avoided by rotating the injection site [*see Dosage and Administration (2.3)*].

As with any protein, local or systemic allergic reactions may occur. Parents/Patients should be informed that such reactions are possible and that prompt medical attention should be sought if allergic reactions occur.

5.13 Laboratory Tests

Serum levels of inorganic phosphorus, alkaline phosphatase, parathyroid hormone (PTH) and IGF-I may increase after somatropin therapy.

5.14 Pancreatitis

Cases of pancreatitis have been reported rarely in children and adults receiving somatropin treatment, with some evidence supporting a greater risk in children compared with adults. Published literature indicates that girls who have Turner syndrome may be at greater risk than other somatropin-treated children. Pancreatitis should be considered in any somatropin-treated patient, especially a child, who develops persistent severe abdominal pain.

6 ADVERSE REACTIONS

6.1 Most Serious and/or Most Frequently Observed Adverse Reactions

This list presents the most serious^b and/or most frequently observed^a adverse reactions during treatment with somatropin:

- ^bSudden death in pediatric patients with Prader-Willi syndrome with risk factors including severe obesity, history of upper airway obstruction or sleep apnea and unidentified respiratory infection [*see Contraindications (4.2) and Warnings and Precautions (5.2)*]
- ^bIntracranial tumors, in particular meningiomas, in teenagers/young adults treated with radiation to the head as children for a first neoplasm and somatropin [*see Contraindications (4.3) and Warnings and Precautions (5.3)*]

- ^{a,b}Glucose intolerance including impaired glucose tolerance/impaired fasting glucose as well as overt diabetes mellitus [*see Warnings and Precautions (5.4)*]
- ^bIntracranial hypertension [*see Warnings and Precautions (5.5)*]
- ^bSignificant diabetic retinopathy [*see Contraindications (4.4)*]
- ^bSlipped capital femoral epiphysis in pediatric patients [*see Warnings and Precautions (5.8)*]
- ^bProgression of preexisting scoliosis in pediatric patients [*see Warnings and Precautions (5.9)*]
- ^aFluid retention manifested by edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome/paraesthesias [*see Warnings and Precautions (5.6)*]
- ^aUnmasking of latent central hypothyroidism [*see Warnings and Precautions (5.7)*]
- ^aInjection site reactions/rashes and lipoatrophy (as well as rare generalized hypersensitivity reactions) [*see Warnings and Precautions (5.12)*]
- Pancreatitis [*see Warnings and Precautions (5.14)*]

6.2 Clinical Trials Experience

Because clinical trials are conducted under varying conditions, adverse reaction rates observed during the clinical trials performed with one somatotropin formulation cannot always be directly compared to the rates observed during the clinical trials performed with a second somatotropin formulation, and may not reflect the adverse reaction rates observed in practice.

Clinical Trials in Children with Noonan Syndrome

Norditropin was studied in a two-year prospective, randomized, parallel dose group trial in 21 children, 3-14 years old, with Noonan syndrome. Doses were 0.033 and 0.066 mg/kg/day. After the initial two-year randomized trial, children continued Norditropin treatment until final height was achieved; randomized dose groups were not maintained. Final height and adverse event data were later collected retrospectively from 18 children; total follow-up was 11 years. An additional 6 children were not randomized, but followed the protocol and are included in this assessment of adverse events.

Based on the mean dose per treatment group, no significant difference in the incidence of adverse events was seen between the two groups. The most frequent adverse events were the common infections of childhood, including upper respiratory infection, gastroenteritis, ear infection, and influenza. Cardiac disorders was the system organ class with the second most adverse events reported. However, congenital heart disease is an inherent component of Noonan syndrome, and there was no evidence of somatotropin-induced ventricular hypertrophy or exacerbation of preexisting ventricular hypertrophy (as judged by echocardiography) during this study. Children who had baseline cardiac disease judged to be significant enough to potentially affect growth were excluded from the study; therefore the safety of Norditropin in children with Noonan syndrome and significant cardiac disease is not known. Among children who received 0.033 mg/kg/day, there was one adverse event of scoliosis; among children who received 0.066 mg/kg/day, there were four adverse events of scoliosis [*see Warnings and Precautions (5.9)*]. Mean serum IGF-I standard deviation score (SDS) levels did not exceed +1 in response to somatotropin treatment. The mean serum IGF-I level was low at baseline and normalized during treatment.

Clinical Trials in Children with Turner Syndrome

In two clinical studies wherein children with Turner syndrome were treated until final height with various doses of Norditropin as described in *Clinical Studies (14.2)*, the most frequently reported adverse events were common childhood diseases including influenza-like illness, otitis media, upper respiratory tract infection, otitis externa, gastroenteritis and eczema. Otitis media adverse events in Study 1 were most frequent in the highest dose groups (86.4% in the 0.045-0.067-0.089 mg/kg/day group vs. 78.3% in the 0.045-0.067 mg/kg/day group vs. 69.6% in the 0.045 mg/kg/day group) suggesting a possible dose-response relationship. Of note, approximately 40-50% of these otitis media adverse events were designated as "serious" [see *Warnings and Precautions (5.10)*]. No patients in either study developed clearcut overt diabetes mellitus; however, in Study 1, impaired fasting glucose at Month 48 was more frequent in patients in the 0.045-0.067 mg/kg/day group (n=4/18) compared with the 0.045 mg/kg/day group (n=1/20). Transient episodes of fasting blood sugars between 100 and 126 mg/dL, and, on occasion, exceeding 126 mg/dL also occurred more often with larger doses of Norditropin in both studies [see *Warnings and Precautions (5.4)* and *Adverse Reactions (6.1)*]. Three patients withdrew from the 2 high dose groups in Study 1 because of concern about excessive growth of hands or feet. In addition, in Study 1, exacerbation of preexisting scoliosis was designated a serious adverse reaction in two patients in the 0.045 mg/kg/day group [see *Warnings and Precautions (5.9)*].

Clinical Trials in Children Born Small for Gestational Age (SGA) with No Catch-up Growth by Age 2-4 Years

Study 1 (Long-Term)

In a multi-center, randomized, double-blind study, 53 non-GHD children with short stature born SGA with failure to catch-up were treated with 2 doses of Norditropin (0.033 or 0.067 mg/kg/day) to final height for up to 13 years (mean duration of treatment 7.9 and 9.5 years for girls and boys, respectively). The most frequently reported adverse events were common childhood diseases including influenza-like illness, upper respiratory tract infection, bronchitis, gastroenteritis, abdominal pain, otitis media, pharyngitis, arthralgia, and headache. Adverse events possibly/probably related to Norditropin were otitis media, arthralgia, headaches (no confirmed diagnoses of benign intracranial hypertension), gynecomastia, and increased sweating. One child treated with 0.067 mg/kg/day for 4 years was reported with disproportionate growth of the lower jaw, and another child treated with 0.067 mg/kg/day developed a melanocytic nevus [see *Warnings and Precautions (5.3)*]. There were no clear cut reports of exacerbation of preexisting scoliosis or slipped capital femoral epiphysis. No apparent differences between the treatment groups were observed. In addition, the timing of puberty was age-appropriate in boys and girls in both treatment groups. Therefore, it can be concluded that no novel adverse events potentially related to treatment with Norditropin were reported in long-term Study 1.

Study 2 (Short-Term)

In a multi-center, randomized, double-blind, parallel-group study, 98 Japanese non-GHD children with short stature born SGA with failure to catch-up were treated with 2 doses of Norditropin (0.033 or 0.067 mg/kg/day) for 2 years or were untreated for 1 year. The most frequently reported adverse events were common childhood diseases almost identical to those reported above for Study 1. Adverse events possibly/probably related to Norditropin were otitis media, arthralgia and impaired glucose tolerance. No apparent differences between the treatment groups were observed. However, arthralgia and transiently impaired glucose tolerance were only reported in the 0.067 mg/kg/day

treatment group. Therefore, it can also be concluded that no novel adverse events potentially related to treatment with rhGH were reported in short-term Study 2.

As with all protein drugs, some patients may develop antibodies to the protein. Eighteen of the 76 children (~24%) treated with Norditropin developed anti-rhGH antibodies. However, these antibodies did not appear to be neutralizing in that the change from baseline in height SDS at Year 2 was similar in antibody positive and antibody negative children by treatment group.

In both Study 1 and Study 2, there were no clear cut cases of new onset diabetes mellitus, no children treated for hyperglycemia, and no adverse event withdrawals due to abnormalities in glucose tolerance. In Study 2, after treatment with either dose of Norditropin for 2 years, there were no children with consecutive fasting blood glucose levels between 100 and 126 mg/dL, or with fasting blood glucose levels > 126 mg/dL. Furthermore, mean hemoglobin A1c levels tended to decrease during long-term treatment in Study 1, and remained normal in Study 2. However, in Study 1, 4 children treated with 0.067 mg/kg/day of Norditropin and 2 children treated with 0.033 mg/kg/day of Norditropin shifted from normal fasting blood glucose levels at baseline to increased levels after 1 year of treatment (100 to 126 mg/dL or > 126 mg/dL). In addition, small increases in mean fasting blood glucose and insulin levels (within the normal reference range) after 1 and 2 years of Norditropin treatment appeared to be dose-dependent [*see Warnings and Precautions (5.4) and Adverse Reactions (6.1)*].

In both Study 1 and Study 2, there was no acceleration of bone maturation. A dose-dependent increase in mean serum IGF-I SDS levels within the reference range (but including a substantial number of children with serum IGF-1 SDS > +2) was observed after both long-term (Study 1) and short-term (Study 2) Norditropin treatment.

Clinical Trials in Adult GHD Patients

Adverse events with an incidence of ^{35%} occurring in patients with AO GHD during the 6 month placebo-controlled portion of the largest of the six adult GHD Norditropin trials are presented in Table 1. Peripheral edema, other types of edema, arthralgia, myalgia, and paraesthesia were common in the Norditropin-treated patients, and reported much more frequently than in the placebo group. These types of adverse events are thought to be related to the fluid accumulating effects of somatotropin. In general, these adverse events were mild and transient in nature. During the placebo-controlled portion of this study, approximately 5% of patients without preexisting diabetes mellitus treated with Norditropin were diagnosed with overt type 2 diabetes mellitus compared with none in the placebo group [*see Warnings and Precautions (5.4) and Adverse Reactions (6.1)*]. Anti-GH antibodies were not detected.

Of note, the doses of Norditropin employed during this study (completed in the mid 1990s) were substantially larger than those currently recommended by the Growth Hormone Research Society, and, more than likely, resulted in a greater than expected incidence of fluid retention- and glucose intolerance-related adverse events. A similar incidence and pattern of adverse events were observed during the other three placebo-controlled AO GHD trials and during the two placebo-controlled CO GHD trials.

Table 1 – Adverse Reactions with ≥5% Overall Incidence in Adult Onset Growth Hormone Deficient Patients Treated with Norditropin During a Six Month Placebo-

Controlled Clinical Trial

Norditropin

(N=53) Placebo

		(N=52)			
		Adverse Reactions		n	%
		n	%		
Peripheral Edema		22	42	4	8
Edema	13	25	0	0	
Arthralgia	10	19	8	15	
Leg Edema	8	15	2	4	
Myalgia	8	15	4	8	
Infection (non-viral)	7	13	4	8	
Paraesthesia	6	11	3	6	
Skeletal Pain	6	11	1	2	
Headache	5	9	3	6	
Bronchitis	5	9	0	0	
Flu-like symptoms	4	8	2	4	
Hypertension	4	8	1	2	
Gastroenteritis	4	8	4	8	
Other Non-Classifiable Disorders (excludes accidental injury)			4	8	3 6
Increased sweating	4	8	1	2	
Glucose tolerance abnormal		3	6	1	2
Laryngitis	3	6	3	6	

The adverse event pattern observed during the open label phase of the study was similar to the one presented above.

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Norditropin with the incidence of antibodies to other products may be misleading. In the case of growth hormone, antibodies with binding capacities lower than 2 mg/mL have not been associated with growth attenuation. In a very small number of patients treated with somatropin, when binding capacity was greater than 2 mg/mL, interference with the growth response was observed.

In clinical trials, GHD pediatric patients receiving Norditropin for up to 12 months were tested for induction of antibodies, and 0/358 patients developed antibodies with binding capacities above 2 mg/L. Amongst these patients, 165 had previously been treated with other somatropin formulations, and 193 were previously untreated naive patients.

6.3 Post-Marketing Experience

Because these adverse events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The adverse events reported during post-marketing surveillance do not differ from those listed/discussed above in Sections 6.1 and 6.2 in

children and adults.

Leukemia has been reported in a small number of GH deficient children treated with somatropin, somatrem (methionylated rhGH) and GH of pituitary origin. It is uncertain whether these cases of leukemia are related to GH therapy, the pathology of GHD itself, or other associated treatments such as radiation therapy. On the basis of current evidence, experts have not been able to conclude that GH therapy *per se* was responsible for these cases of leukemia. The risk for children with GHD, if any, remains to be established [see *Contraindications (4.3) and Warnings and Precautions (5.3)*].

The following additional adverse reactions have been observed during the appropriate use of somatropin: headaches (children and adults), gynecomastia (children), and pancreatitis (children and adults [see *Warnings and Precautions (5.14)*]).

New-onset type 2 diabetes mellitus has been reported.

7 DRUG INTERACTIONS

7.1 Inhibition of 11 β -Hydroxysteroid Dehydrogenase Type 1 (11 β HSD-1)

The microsomal enzyme 11 β -hydroxysteroid dehydrogenase type 1 (11 β HSD-1) is required for conversion of cortisone to its active metabolite, cortisol, in hepatic and adipose tissue. GH and somatropin inhibit 11 β HSD-1. Consequently, individuals with untreated GHD have relative increases in 11 β HSD-1 and serum cortisol. Introduction of somatropin treatment may result in inhibition of 11 β HSD-1 and reduced serum cortisol concentrations. As a consequence, previously undiagnosed central (secondary) hypoadrenalism may be unmasked and glucocorticoid replacement may be required in patients treated with somatropin. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of somatropin treatment; this may be especially true for patients treated with cortisone acetate and prednisone since conversion of these drugs to their biologically active metabolites is dependent on the activity of 11 β HSD-1.

7.2 Pharmacologic Glucocorticoid Therapy and Supraphysiologic Glucocorticoid Treatment

Pharmacologic glucocorticoid therapy and supraphysiologic glucocorticoid treatment may attenuate the growth promoting effects of somatropin in children. Therefore, glucocorticoid replacement dosing should be carefully adjusted in children receiving concomitant somatropin and glucocorticoid treatments to avoid both hypoadrenalism and an inhibitory effect on growth.

7.3 Cytochrome P450-Metabolized Drugs

Limited published data indicate that somatropin treatment increases cytochrome P450 (CYP450)- mediated antipyrine clearance in man. These data suggest that somatropin administration may alter the clearance of compounds known to be metabolized by CYP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporine). Careful monitoring is advisable when somatropin is administered in combination with other drugs known to be metabolized by CYP450 liver enzymes. However, formal drug interaction studies have not been conducted.

7.4 Oral Estrogen

Because oral estrogens may reduce the serum IGF-1 response to somatropin treatment, girls and women receiving oral estrogen replacement may require greater somatropin

dosages [see *Dosage and Administration (2.2)*].

7.5 Insulin and/or Oral/Injectable Hypoglycemic Agents

In patients with diabetes mellitus requiring drug therapy, the dose of insulin and/or oral/injectable agent may require adjustment when somatropin therapy is initiated [see *Warnings and Precautions (5.4)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Norditropin. It is not known whether Norditropin can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Norditropin should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether Norditropin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Norditropin is administered to a nursing woman.

8.5 Geriatric Use

The safety and effectiveness of Norditropin in patients aged 65 and over has not been evaluated in clinical studies. Elderly patients may be more sensitive to the action of somatropin, and therefore may be more prone to develop adverse reactions. A lower starting dose and smaller dose increments should be considered for older patients [see *Dosage and Administration (2.2)*].

10. OVERDOSAGE

Short-Term

Short-term overdosage could lead initially to hypoglycemia and subsequently to hyperglycemia. Furthermore, overdose with somatropin is likely to cause fluid retention.

Long-Term

Long-term overdosage could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess growth hormone [see *Dosage and Administration (2)*].

11 DESCRIPTION

Norditropin is a polypeptide hormone of recombinant DNA origin. The hormone is synthesized by a special strain of *E. coli* bacteria that has been modified by the addition of a plasmid which carries the gene for human growth hormone. Norditropin contains the identical sequence of 191 amino acids constituting the naturally occurring pituitary human growth hormone with a molecular weight of about 22,000 Daltons.

Norditropin cartridges are supplied as sterile solutions for subcutaneous injection in ready-to-administer cartridges or prefilled pens with a volume of 1.5 mL or 3 mL.

Each **Norditropin Cartridge** contains the following (see Table 2):

Table 2

Component	5 mg/1.5 mL	10 mg/1.5 mL	15 mg/1.5 mL	30 mg/3 mL
Somatropin	5 mg	10 mg	15 mg	30 mg
Histidine	1 mg	1 mg	1.7 mg	3.3 mg
Poloxamer 188	4.5 mg	4.5 mg	4.5 mg	9.0 mg
Phenol	4.5 mg	4.5 mg	4.5 mg	9.0 mg
Mannitol	60 mg	60 mg	58 mg	117 mg
HCl/NaOH	as needed	as needed	as needed	as needed
Water for Injection	up to 1.5 mL	up to 1.5 mL	up to 1.5 mL	up to 3.0 mL

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Somatropin (as well as endogenous GH) binds to a dimeric GH receptor in the cell membrane of target cells resulting in intracellular signal transduction and a host of pharmacodynamic effects. Some of these pharmacodynamic effects are primarily mediated by IGF-I produced in the liver and also locally (e.g., skeletal growth, protein synthesis), while others are primarily a consequence of the direct effects of somatropin (e.g., lipolysis) [see *Clinical Pharmacology (12.2)*].

12.2 Pharmacodynamics

Tissue Growth

The primary and most intensively studied action of somatropin is the stimulation of linear growth. This effect is demonstrated in children with GHD.

Skeletal Growth

The measurable increase in bone length after administration of somatropin results from its effect on the cartilaginous growth areas of long bones. Studies *in vitro* have shown that the incorporation of sulfate into proteoglycans is not due to a direct effect of somatropin, but rather is mediated by the somatomedins or insulin-like growth factors (IGFs). The somatomedins, among them IGF-I, are polypeptide hormones which are synthesized in the liver, kidney, and various other tissues. IGF-I levels are low in the serum of hypopituitary dwarfs and hypophysectomized humans or animals, and increase after treatment with somatropin.

Cell Growth

It has been shown that the total number of skeletal muscle cells is markedly decreased in children with short stature lacking endogenous GH compared with normal children, and that treatment with somatropin results in an increase in both the number and size of muscle cells.

Organ Growth

Somatropin influences the size of internal organs, and it also increases red cell mass.

Protein Metabolism

Linear growth is facilitated in part by increased cellular protein synthesis. This synthesis and growth are reflected by nitrogen retention which can be quantitated by observing the decline in urinary nitrogen excretion and blood urea nitrogen following the initiation of somatropin therapy.

Carbohydrate Metabolism

Hypopituitary children sometimes experience fasting hypoglycemia that may be improved by treatment with somatropin. In healthy subjects, large doses of somatropin may impair glucose tolerance. Although the precise mechanism of the diabetogenic effect of

somatropin is not known, it is attributed to blocking the action of insulin rather than blocking insulin secretion. Insulin levels in serum actually increase as somatropin levels increase. Administration of human growth hormone to normal adults and patients with growth hormone deficiency results in increases in mean serum fasting and postprandial insulin levels, although mean values remain in the normal range. In addition, mean fasting and postprandial glucose and hemoglobin A_{1c} levels remain in the normal range.

Lipid Metabolism

Somatropin stimulates intracellular lipolysis, and administration of somatropin leads to an increase in plasma free fatty acids and triglycerides. Untreated GHD is associated with increased body fat stores, including increased abdominal visceral and subcutaneous adipose tissue. Treatment of growth hormone deficient patients with somatropin results in a general reduction of fat stores, and decreased serum levels of low density lipoprotein (LDL) cholesterol.

Mineral Metabolism

Administration of somatropin results in an increase in total body potassium and phosphorus and to a lesser extent sodium. This retention is thought to be the result of cell growth. Serum levels of phosphate increase in children with GHD after somatropin therapy due to metabolic activity associated with bone growth. Serum calcium levels are not altered. Although calcium excretion in the urine is increased, there is a simultaneous increase in calcium absorption from the intestine. Negative calcium balance, however, may occasionally occur during somatropin treatment.

Connective Tissue Metabolism

Somatropin stimulates the synthesis of chondroitin sulfate and collagen, and increases the urinary excretion of hydroxyproline.

12.3 Pharmacokinetics

A 180-min IV infusion of Norditropin (33 ng/kg/min) was administered to 9 GHD patients. A mean (\pm SD) hGH steady state serum level of approximately 23.1 (\pm 15.0) ng/mL was reached at 150 min and a mean clearance rate of approximately 2.3 (\pm 1.8) mL/min/kg or 139 (\pm 105) mL/min for hGH was observed. Following infusion, serum hGH levels had a biexponential decay with a terminal elimination half-life ($T_{1/2}$) of approximately 21.1 (\pm 5.1) min.

In a study conducted in 18 GHD adult patients, where a SC dose of 0.024 mg/kg or 3 IU/m² was given in the thigh, mean (\pm SD) C_{max} values of 13.8 (\pm 5.8) and 17.1 (\pm 10.0) ng/mL were observed for the 4 and 8 mg Norditropin vials, respectively, at approximately 4 to 5 hr. post dose. The mean apparent terminal $T_{1/2}$ values were estimated to be approximately 7 to 10 hr. However, the absolute bioavailability for Norditropin after the SC route of administration is currently not known.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and fertility studies have not been conducted with Norditropin.

14. CLINICAL STUDIES

14.1 Short Stature in Children with Noonan Syndrome

A prospective, open label, randomized, parallel group trial with 21 children was conducted for 2 years to evaluate the efficacy and safety of Norditropin treatment for short stature in children with Noonan syndrome. An additional 6 children were not randomized, but did follow the protocol. After the initial two-year trial, children continued on Norditropin until final height. Retrospective final height and adverse event data were collected from 18 of the 21 subjects who were originally enrolled in the trial and the 6 who had followed the protocol without randomization. Historical reference materials of height velocity and adult height analyses of Noonan patients served as the controls.

The twenty-four (24) (12 female, 12 male) children 3 – 14 years of age received either 0.033 mg/kg/day or 0.066 mg/kg/day of Norditropin subcutaneously which, after the first 2 years, was adjusted based on growth response.

In addition to a diagnosis of Noonan syndrome, key inclusion criteria included bone age determination showing no significant acceleration, prepubertal status, height SDS <-2, and HV SDS <1 during the 12 months pre-treatment. Exclusion criteria were previous or ongoing treatment with growth hormone, anabolic steroids or corticosteroids, congenital heart disease or other serious disease perceived to possibly have major impact on growth, FPG >6.7 mmol/L (>120 mg/dL), or growth hormone deficiency (peak GH levels <10 ng/mL).

Patients obtained a final height (FH) gain from baseline of 1.5 and 1.6 SDS estimated according to the national and the Noonan reference, respectively. A height gain of 1.5 SDS (national) corresponds to a mean height gain of 9.9 cm in boys and 9.1 cm in girls at 18 years of age, while a height gain of 1.6 SDS (Noonan) corresponds to a mean height gain of 11.5 cm in boys and 11.0 cm in girls at 18 years of age.

A comparison of HV between the two treatment groups during the first two years of treatment for the randomized subjects was 10.1 and 7.6 cm/year with 0.066 mg/kg/day versus 8.55 and 6.7 cm/year with 0.033 mg/kg/day, for Year 1 and Year 2, respectively.

Age at start of treatment was a factor for change in height SDS (national reference). The younger the age at start of treatment, the larger the change in height SDS.

Examination of gender subgroups did not identify differences in response to Norditropin. Not all patients with Noonan syndrome have short stature; some will achieve a normal adult height without treatment. Therefore, prior to initiating Norditropin for a patient with Noonan syndrome, establish that the patient does have short stature.

14.2 Short Stature in Children with Turner Syndrome

Two randomized, parallel group, open label, multicenter studies were conducted in the Netherlands to evaluate the efficacy and safety of Norditropin for the treatment of children with short stature associated with Turner syndrome. Patients were treated to final height in both studies [height velocity (HV) < 2 cm/year]. Changes in height were expressed as standard deviation scores (SDS) utilizing reference data for untreated Turner syndrome patients as well as the national Dutch population.

In Study 1 (the primary study), 68 euthyroid Caucasian patients stratified based on age and baseline height SDS were randomized in a 1:1:1 ratio to three different Norditropin treatment regimens: 0.045 mg/kg/day (Dose A) for the entire study; 0.045 mg/kg/day for the first year and 0.067 mg/kg/day thereafter (Dose B); or 0.045 mg/kg/day for the first year, 0.067 for the second year, and 0.089 mg/kg/day thereafter (Dose C). Overall, at baseline, mean age was 6.5 years, mean height SDS (National standard) was -2.7, and mean HV during the previous year was 6.5 cm/year. Patients also received estrogen therapy after age 12 and following four years of Norditropin treatment if they did not have spontaneous puberty.

Patients were treated for a mean of 8.4 years. As seen in Table 3, overall mean final height was 161 cm in the 46 children who attained final height. Seventy percent of these children reached a final height within the normal range (height SDS > -2 using the National standard). A greater percentage of children in the two escalated dose groups reached normal final height. The mean changes from baseline to final height in height SDS after treatment with Dose B and Dose C were significantly greater than the mean changes observed after treatment with Dose A (utilizing both the National and Turner standards). The mean changes from baseline to final height in height SDS (Turner standard) in Table 3 correspond to mean height gains of 9.4, 14.1 and 14.4 cm after treatment with Doses A, B and C, respectively. The mean changes from baseline to final height in height SDS (National standard) in Table 3 correspond to mean height gains of 4.5, 9.1 and 9.4 cm after treatment with Doses A, B and C, respectively. In each treatment group, peak HV was observed during treatment Year 1, and then gradually decreased each year; during Year 4, HV was less than the pre-treatment HV. However, between Year 2 and Year 6, a greater HV was observed in the two dose escalation groups compared to the 0.045 mg/kg/day group.

Table 3 – Final Height-Related Results After Treatment of Patients with Turner Syndrome with Norditropin in a Randomized, Dose Escalating Study
Dose A

	0.045 mg/kg/day			
	(n = 19)		Dose B	
	up to 0.067 mg/kg/day			
	(n = 15)		Dose C	
	up to 0.089 mg/kg/day			
	(n = 12)			
	Total (n = 46)			
Baseline height (cm) ¹	105 (12)	108 (12.7)	107 (11.7)	106 (11.9)
Final height (cm) ¹	157 (6.7)	163 (6.0)	163 (4.9)	161 (6.5)
Number (%) of patients reaching normal height (height SDS > -2 using National standard)	10 (53%)	12 (80%)	10 (83%)	32 (70%)
	Height SDS (Turner standard) ²			

Final [95% CI]	1.7 [1.4, 2.0]	2.5 [2.1, 2.8] ³	2.5 [2.1, 2.9] ⁴	NA
Change from baseline [95% CI]	1.5 [1.2, 1.8]	2.2 [1.9, 2.5] ³	2.2 [1.9, 2.6] ⁴	NA
	Height SDS (National standard) ²			
Final [95% CI]	-1.9 [-2.2, -1.6]	-1.2 [-1.5, -0.9] ⁴	-1.2 [-1.6, -0.8] ⁵	NA
Change from baseline [95% CI]	0.7 [0.4, 1.0]	1.4 [1.1, 1.7] ⁴	1.4 [1.1, 1.8] ⁵	NA

Values are expressed as mean (SD) unless otherwise indicated. SDS: Standard deviation score.

¹Unadjusted (raw) means; ²Adjusted (least squares) means based on an ANCOVA model including terms for treatment, duration of treatment, age at baseline, bone age at baseline, height SDS at baseline, age at onset of puberty and mid-parental target height SDS;

³p=0.005 vs. Dose A; ⁴p=0.006 vs. Dose A; ⁵p=0.008 vs. Dose A

In Study 2 (a supportive study), 19 euthyroid Caucasian patients (with bone age \leq 13.9 years) were randomized to treatment with 0.067 mg/kg/day of Norditropin as a single subcutaneous dose in the evening, or divided into two doses (1/3 morning and 2/3 evening). All subjects were treated with concomitant ethinyl estradiol. Overall, at baseline, mean age was 13.6 years, mean height SDS (National standard) was -3.5 and mean HV during the previous year was 4.3 cm/year. Patients were treated for a mean of 3.6 years. In that there were no significant differences between the two treatment groups for any linear growth variables, the data from all patients were pooled. Overall mean final height was 155 cm in the 17 children who attained final height. Height SDS changed significantly from

-3.5 at baseline to -2.4 at final height (National standard), and from 0.7 to 1.3 at final height (Turner standard).

14.3 Short Stature in Children Born Small for Gestational Age (SGA) with No Catch-up Growth by Age 2-4 Years

A multi-center, randomized, double-blind, two-arm study to final height (Study 1) and a 2-year, multi-center, randomized, double-blind, parallel-group study (Study 2) were conducted to assess the efficacy and safety of Norditropin in children with short stature born SGA with no catch-up growth. Changes in height and height velocity were compared to a national reference population in both studies.

Study 1

The pivotal study included 53 (38 male, 15 female) non-GHD, Dutch children 3-11 years of age with short stature born SGA with no catch-up growth. Catch-up growth was defined as obtaining a height of \geq 3rd percentile within the first 2 years of life or at a later stage. These prepubertal children needed to meet the following additional inclusion criteria: birth length < 3rd percentile for gestational age, and height velocity (cm/year) for chronological age < 50th percentile. Exclusion criteria included chromosomal abnormalities, signs of a syndrome (except for Silver-Russell syndrome), serious/chronic co-morbid disease, malignancy, and previous rhGH therapy. Norditropin was administered subcutaneously daily at bedtime at a dose of approximately 0.033 (Dose A) or 0.067 mg/kg/day (Dose B) for the entire treatment period. Final height was defined as a height velocity below 2 cm/year. Treatment with Norditropin was continued to final height for up to 13 years. Mean duration of treatment was 9.5 years (boys) and 7.9 years (girls).

38 out of 53 children (72%) reached final height. Sixty-three percent (24 out of 38) of the children who reached final height were within the normal range of their healthy peers (Dutch national reference). For both doses combined, actual mean final height was 171 (SD 6.1) cm in boys and 159 (SD 4.3) cm in girls.

As seen in Table 4, for boys and girls combined, both mean final height SDS (Dose A, -1.8 vs. Dose B, -1.3), and increase in height SDS from baseline to final height (Dose A, 1.4 vs. Dose B, 1.8), were significantly greater after treatment with Dose B (0.067 mg/kg/day). A similar dose response was observed for the increase in height SDS from baseline to Year 2 (Table 4).

Overall mean height velocity at baseline was 5.4 cm/y (SD 1.2; n=29). Height velocity was greatest during the first year of Norditropin treatment and was significantly greater after treatment with Dose B (mean 11.1 cm/y [SD 1.9; n=19]) compared with Dose A (mean 9.7 cm/y [SD 1.3; n=10]).

Table 4 – Study 1: Results for Final Height SDS and Change from Baseline to Final Height in Height SDS Using National Standard After Long-Term Treatment of SGA Children with Norditropin

Raw Mean ± SD (N)

Dose A

0.033 mg/kg/day Dose B

0.067 mg/kg/day

Total

Baseline Height SDS -3.2 ± 0.7 (26) -3.2 ± 0.7 (27) -3.2 ± 0.7 (53)

Adjusted least-squares mean ± standard error (N) and [95% confidence intervals]

Height SDS: Change from Baseline at Year 2² 1.4 ± 0.1 (26)

[1.1, 1.6] 1.8 ± 0.1 (26)

[1.5, 2.0] Treatment Diff = 0.4

[0.2, 0.7]

p-value = 0.002

Height SDS: Change from Baseline at Final Height¹ 1.4 ± 0.2 (19)

[0.9, 1.8] 1.8 ± 0.2 (19)

[1.4, 2.2] Treatment Diff = 0.5

[0.0, 0.9]

p-value = 0.045

Final Height SDS¹ -1.8 ± 0.2 (19)

[-2.2, -1.4] -1.3 ± 0.2 (19)

[-1.7, -0.9]

Final Height SDS > -2 13/19 (68%) 11/19 (58%) 24/38 (63%)
SDS: Standard deviation score.

¹Adjusted (least-squares) means based on an ANCOVA model including terms for treatment, gender, age at baseline, bone age at baseline, height SDS at baseline, duration of treatment, peak GH after stimulation and baseline IGF-1.

²Adjusted (least-squares) means based on an ANCOVA model including terms for treatment, gender, age at baseline, height SDS at baseline, and pubertal status.

Study 2

In this study, 84 randomized, prepubertal, non-GHD, Japanese children (age 3-8) with short stature born SGA with no catch-up growth were treated for 2 years with 0.033 or 0.067 mg/kg/day of Norditropin subcutaneously daily at bedtime or received no treatment for 1 year. Additional inclusion criteria included birth length or weight SDS ≤ -2 or < 10th percentile for gestational age, height SDS for chronological age ≤ -2, and height velocity SDS for chronological age < 0 within one year prior to Visit 1. Exclusion criteria included diabetes mellitus, history or presence of active malignancy, and serious co-morbid conditions.

As seen in Table 5, for boys and girls combined, there was a dose-dependent increase in height SDS at Year 1 and Year 2. The increase in height SDS from baseline to Year 2 (0.033 mg/kg/day, 0.8 vs. 0.067 mg/kg/day, 1.4) was significantly greater after treatment with 0.067 mg/kg/day. In addition, the increase in height SDS at Year 1 was significantly greater in both active treatment groups compared to the untreated control group.

Table 5 – Study 2: Results for Change from Baseline in Height SDS At Year 1 and Year 2 Using National Standard After Short-Term Treatment of SGA Children with Norditropin

	Raw Mean ± SD (N)			
	No Treatment	0.033 mg/kg/day	0.067 mg/kg/day	Total
Height SDS: Baseline	-2.9 ± 0.5 (15)	-3.0 ± 0.6 (35)	-2.9 ± 0.7 (34)	-2.9 ± 0.6 (84)
Height SDS: Year 1	-2.8 ± 0.5 (15)	-2.4 ± 0.6 (33)	-2.0 ± 0.8 (34)	-2.3 ± 0.7 (82)
Height SDS: Year 2	NA	-2.2 ± 0.7 (33)	-1.4 ± 0.7 (32)	-1.8 ± 0.8 (65)
	Adjusted least-squares mean ± standard error (N) and [95% confidence intervals]			
Height SDS: Change from Baseline at Year 1 ¹		0.1 ± 0.1 (15)		
	[-0.1, 0.2]	0.6 ± 0.1 (33)		
	[0.5, 0.7]	0.9 ± 0.1 (34)		
	[0.8, 1.0]			

0.033 vs. No Treatment: Treatment Diff = 0.5, [0.3, 0.7], p < 0.0001

0.067 vs. No Treatment: Treatment Diff = 0.8, [0.6, 1.0], p < 0.0001

0.067 vs. 0.033: Treatment Diff = 0.3, [0.2, 0.5], p-value < 0.0001

Height SDS: Change from Baseline at Year 2¹ NA 0.8 ± 0.1 (33)

[0.7, 0.9] 1.4 ± 0.1 (32)

[1.3, 1.6]

0.067 vs. 0.033: Treatment Diff = 0.6, [0.5, 0.8], p-value < 0.0001

SDS: Standard deviation score.

¹Adjusted (least-squares) means based on an ANCOVA model including terms for treatment, gender, age at baseline, and height SDS at baseline. All children remained prepubertal during the study.

14.4 Adult Growth Hormone Deficiency (GHD)

A total of six randomized, double-blind, placebo-controlled studies were performed. Two representative studies, one in adult onset (AO) GHD patients and a second in childhood onset (CO) GHD patients, are described below.

Study 1

A single center, randomized, double-blind, placebo-controlled, parallel-group, six month clinical trial was conducted in 31 adults with AO GHD comparing the effects of Norditropin [somatotropin (rDNA origin) for injection] and placebo on body composition. Patients in the active treatment arm were treated with Norditropin 0.017 mg/kg/day (not to exceed 1.33 mg/day). The changes from baseline in lean body mass (LBM) and percent total body fat (TBF) were measured by total body potassium (TBP) after 6 months.

Treatment with Norditropin produced a significant (p=0.0028) increase from baseline in LBM compared to placebo (Table 6).

Table 6 – Lean Body Mass (kg) by TBP

	Norditropin	Placebo
	(n=15)	(n=16)
Baseline (mean)	50.27	51.72
Change from baseline at 6 months (mean)	1.12	-0.63
Treatment difference (mean)		
95% confidence interval		
p-value	1.74	
	(0.65, 2.83)	
	p=0.0028	

Analysis of the treatment difference on the change from baseline in percent TBF revealed a significant decrease ($p=0.0004$) in the Norditropin-treated group compared to the placebo group (Table 7).

Table 7 – Total Body Fat (%) by TBP

	Norditropin		
	(n=15) Placebo		
	(n=16)		
	Baseline (mean)	44.74	42.26
	Change from baseline at 6 months (mean)	-2.83	1.92
	Treatment difference (mean)		
95% confidence interval	(-7.18, -2.30)		
p-value	-4.74		
	p=0.0004		

Fifteen (48.4%) of the 31 randomized patients were male. The adjusted mean treatment differences on the increase in LBM and decrease in percent TBF from baseline were larger in males compared to females.

Norditropin also significantly increased serum osteocalcin (a marker of osteoblastic activity).

Study 2

A single center, randomized, double-blind, placebo-controlled, parallel-group, dose-finding, six month clinical trial was conducted in 49 men with CO GHD comparing the effects of Norditropin and placebo on body composition. Patients were randomized to placebo or one of three active treatment groups (0.008, 0.016, and 0.024 mg/kg/day). Thirty three percent of the total dose to which each patient was randomized was administered during weeks 1-4, 67% during weeks 5-8, and 100% for the remainder of the study. The changes from baseline in LBM and percent TBF were measured by TBP after 6 months.

Treatment with Norditropin produced a significant ($p=0.0079$) increase from baseline in LBM compared to placebo (pooled data) (Table 8).

Table 8 – Lean Body Mass (kg) by TBP

	Norditropin		
	(n=36) Placebo		
	(n=13)		
	Baseline (mean)	48.18	48.90
	Change from baseline at 6 months (mean)	2.06	0.70

Treatment difference (mean)

95% confidence interval
p-value 1.40

(0.39, 2.41)

p=0.0079

Analysis of the treatment difference on the change from baseline in percent TBF revealed a significant decrease (p=0.0048) in the Norditropin-treated groups (pooled data) compared to the placebo group (Table 9).

Table 9 – Total Body Fat (%) by TBP

	Norditropin	Placebo
	(n=36)	(n=13)
Baseline (mean)	34.55	34.07
Change from baseline at 6 months (mean)	-6.00	-1.78
Treatment difference (mean)		

95% confidence interval
p-value -4.24

(-7.11, -1.37)

p=0.0048

Norditropin also significantly reduced intraabdominal, extraperitoneal and total abdominal fat volume, waist/hip ratio and LDL cholesterol, and significantly increased serum osteocalcin.

Forty four men were enrolled in an open label follow up study and treated with Norditropin for as long as 30 additional months. During this period, the reduction in waist/hip ratio achieved during the initial six months of treatment was maintained.

16. HOW SUPPLIED/STORAGE AND HANDLING

Norditropin FlexPro prefilled pens [somatropin (rDNA origin) injection] 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL:

Norditropin FlexPro is individually cartoned in 5 mg/1.5 mL, 10 mg/1.5 mL, or 15 mg/1.5 mL prefilled pens.

- Norditropin FlexPro 5 mg/1.5 mL (orange) NDC 0169-7704-21
- Norditropin FlexPro 10 mg/1.5 mL (blue) NDC 0169-7705-21

- Norditropin FlexPro 15 mg/1.5 mL (green) NDC 0169-7708-21

Norditropin NordiFlex prefilled pens [somatropin (rDNA origin) injection] 5 mg/1.5 mL, 10 mg/1.5 mL, 15 mg/1.5 mL and 30 mg/3 mL:

Norditropin NordiFlex is individually cartoned in 5 mg/1.5 mL, 10 mg/1.5 mL, 15 mg/1.5 mL or 30 mg/3 mL prefilled pens.

- Norditropin NordiFlex 5 mg/1.5 mL (orange) NDC 0169-7704-11
- Norditropin NordiFlex 10 mg/1.5 mL (blue) NDC 0169-7705-11
- Norditropin NordiFlex 15 mg/1.5 mL (green) NDC 0169-7708-11
- Norditropin NordiFlex 30 mg/3 mL (purple) NDC 0169-7703-11

Unused Norditropin NordiFlex and FlexPro prefilled pens must be stored at 2-8°C/36-46°F (refrigerator). Do not freeze. Avoid direct light.

5 mg/1.5 mL (orange) and 10 mg/1.5 mL (blue) prefilled pens:

After the initial injection, a Norditropin FlexPro or Norditropin NordiFlex (5 mg/1.5 mL or 10 mg/1.5 mL) prefilled pen may be **EITHER** stored in the refrigerator (2-8°C/36-46°F) and used within 4 weeks **OR** stored for up to 3 weeks at not more than 25°C (77°F). Discard unused portion.

15 mg/1.5 mL (green) and 30 mg/3 mL (purple) prefilled pens:

After the initial injection, a Norditropin FlexPro 15 mg/1.5 mL or Norditropin NordiFlex (15 mg/1.5 mL or 30 mg/3 mL) prefilled pen must be stored in the refrigerator (2-8°C/36-46°F) and used within 4 weeks. Discard unused portion after 4 weeks.

Norditropin Cartridges [somatropin (rDNA origin) injection] 5 mg/1.5 mL and 15 mg/1.5 mL:

Norditropin is individually cartoned in 5 mg/1.5 mL or 15 mg/1.5 mL cartridges which must be administered using the corresponding color-coded NordiPen delivery system.

- Norditropin Cartridges 5 mg/1.5 mL (orange) NDC 0169-7768-11
- Norditropin Cartridges 15 mg/1.5 mL (green) NDC 0169-7770-11

Unused Norditropin cartridges must be stored at 2-8°C/36-46°F (refrigerator). Do not freeze. Avoid direct light.

5 mg/1.5 mL (orange) cartridges:

After a Norditropin cartridge (5 mg/1.5 mL) has been inserted into its NordiPen delivery system (NordiPen 5), it may be **EITHER** stored in the pen in the refrigerator (2-8°C/36-46°F) and used within 4 weeks **OR** stored for up to 3 weeks at not more than 25°C (77°F). Discard unused portion.

15 mg/1.5 mL (green) cartridges:

After a Norditropin cartridge (15 mg/1.5 mL) has been inserted into its NordiPen delivery system (NordiPen 15), it must be stored in the pen in the refrigerator (2-8°C/36-46°F) and used within 4 weeks. Discard unused portion after 4 weeks.

Table 10 – Storage Options

Norditropin Product Formulation Before Use In-use (After 1st injection)
Storage requirement Storage Option 1

(Refrigeration) Storage Option 2
(Room temperature)

5 mg 2-8 °C/

36-46 °F

Until exp date 2-8 °C/36-46 °F

4 weeks Up to 25°C/77°F

10 mg 3 weeks
2-8 °C/36-46 °F

4 weeks Up to 25°C/77°F

15 mg 3 weeks
2-8 °C/36-46 °F

4 weeks Does Not Apply
30 mg 2-8 °C/36-46 °F

4 weeks Does Not Apply

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

Patients being treated with Norditropin FlexPro or Norditropin NordiFlex prefilled pens, or Norditropin Cartridges, (and/or their parents) should be informed about the potential risks and benefits associated with somatotropin treatment [*in particular, see Adverse Reactions (6.1) for a listing of the most serious and/or most frequently observed adverse reactions associated with somatotropin treatment in children and adults*]. This information is intended to better educate patients (and caregivers); it is not a disclosure of all possible adverse or intended effects.

Patients and caregivers who will administer Norditropin FlexPro or Norditropin NordiFlex prefilled pens, or Norditropin Cartridges, should receive appropriate training and instruction on proper use from the physician or other suitably qualified health care professional. A puncture-resistant container for the disposal of used needles should be strongly recommended. Patients and/or parents should be thoroughly instructed in the importance of proper disposal, and cautioned against any reuse of needles. This information is intended to aid in the safe and effective administration of the medication.

If patients are prescribed Norditropin Cartridges (to be inserted into color-coded NordiPen delivery systems), physicians should instruct patients to read the NordiPen INSTRUCTION booklet provided with the NordiPen delivery systems.

If patients are prescribed Norditropin FlexPro or Norditropin NordiFlex, physicians should instruct patients to read the PATIENT INFORMATION and INSTRUCTIONS FOR USE

leaflets provided with the Norditropin FlexPro and Norditropin NordiFlex prefilled pens.

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Novo Nordisk A/S

DK-2880 Bagsvaerd, Denmark

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NovoSeven RT safely and effectively. See full prescribing information for NovoSeven RT.

NovoSeven® RT Coagulation Factor VIIa (Recombinant) Room Temperature Stable, Lyophilized Powder

For Intravenous Use Only

Initial U.S. Approval: 1999

Warning: Serious thrombotic adverse events are associated with the use of NovoSeven RT outside labeled indications

Arterial and venous thrombotic and thromboembolic events following administration of NovoSeven have been reported during postmarketing surveillance. Clinical studies have shown an increased risk of arterial thromboembolic adverse events with NovoSeven RT when administered outside the current approved indications. Fatal and non-fatal thrombotic events have been reported. Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive NovoSeven RT. Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis. **See WARNINGS AND PRECAUTIONS section of prescribing information.**

Safety and efficacy of NovoSeven RT has not been established outside the approved indications.

-----**RECENT MAJOR CHANGES**-----

Boxed Warning

Warnings and Precautions (5) 1/2010

-----**INDICATIONS AND USAGE**-----

- Treatment of bleeding episodes in hemophilia A or B with inhibitors and in acquired hemophilia (1.1)
- Prevention of bleeding in surgical interventions or invasive procedures in hemophilia A or B with inhibitors and in acquired hemophilia (1.2)
- Treatment of bleeding episodes in congenital FVII deficiency (1.3)
- Prevention of bleeding in surgical interventions or invasive procedures in congenital FVII deficiency (1.4)

-----**DOSAGE AND ADMINISTRATION**-----

• For intravenous bolus injection only. After reconstitution, administer within 3 hours; do not freeze or store in syringes (2.6)

‡— NovoSeven RT should be administered to patients only under the supervision of a physician experienced in the treatment of bleeding disorders (2.1)

Hemophilia A or B with Inhibitors – Bleeding Episodes (2.2)

- 90 micrograms/kg bolus injection every 2 hours until hemostasis is achieved
- Post-hemostatic dosing every 3-6 hours for severe bleeds

Hemophilia A or B with Inhibitors – Surgery (2.2)

- 90 micrograms/kg immediately before surgery and every 2 hours during surgery
- Post-surgical dosing:
 - Minor surgery – 90 micrograms/kg every 2 hours for 48 hours and then every 2-6 hours, until healing has occurred
 - Major surgery – 90 micrograms/kg every 2 hours for the first 5 days and then every 4 hours, until healing has occurred

Congenital FVII Deficiency – Bleeding Episodes or Surgery (2.3)

- 15-30 micrograms/kg every 4-6 hours until hemostasis is achieved

Acquired Hemophilia – Bleeding Episodes or Surgery (2.4)

- 70-90 micrograms/kg every 2-3 hours until hemostasis is achieved

-----**DOSAGE FORMS AND STRENGTHS**-----

- Lyophilized powder in single-use vials: 1, 2, 5, or 8 mg rFVIIa (3)
- After reconstitution with specified volume of histidine diluent, each vial contains 1 mg/mL (1000 micrograms/mL) of recombinant FVIIa (3)

-----**CONTRAINDICATIONS**-----

None (4)

-----**WARNINGS AND PRECAUTIONS**-----

- Thrombotic events of possible or probable relationship to NovoSeven occurred in 0.28% of bleeding episodes treated in clinical trials within the approved indications (5.1)
- Increased risk of arterial thromboembolic adverse events with use of NovoSeven was demonstrated in 2 meta analyses of placebo-controlled clinical trials in populations outside the approved indications (5.2)
- Thrombosis has occurred in women treated with NovoSeven to control post-partum hemorrhage (5.2)
- Factor VII deficient patients should be monitored for prothrombin time (PT) and FVII coagulant activity, and for antibody formation to NovoSeven RT (5.4)
- Administer with caution in patients with known hypersensitivity (5.5)

-----**ADVERSE REACTIONS**-----

In clinical trials, the most common adverse reactions are pyrexia, hemorrhage, injection site reaction, arthralgia, headache, hypertension, hypotension, nausea, vomiting, pain, edema and rash (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at [1-877-668-6777](tel:1-877-668-6777) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----**DRUG INTERACTIONS**-----

- Avoid simultaneous use of NovoSeven RT and PCCs/aPCCs (7.1)
- NovoSeven RT should not be mixed with infusion solutions (7.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised:

08/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SERIOUS THROMBOTIC ADVERSE EVENTS

1 INDICATIONS AND USAGE

- 1.1 Hemophilia A or B with inhibitors or Acquired Hemophilia - bleeding episodes
- 1.2 Hemophilia A or B with inhibitors or Acquired Hemophilia - surgery
- 1.3 Congenital FVII deficiency - bleeding episodes
- 1.4 Congenital FVII deficiency - surgery

2 DOSAGE AND ADMINISTRATION

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

FULL PRESCRIBING INFORMATION

Warning: Serious thrombotic adverse events are associated with the use of NovoSeven RT outside labeled indications

Arterial and venous thrombotic and thromboembolic events following administration of NovoSeven have been reported during postmarketing surveillance. Clinical studies have shown an increased risk of arterial thromboembolic adverse events with NovoSeven RT when administered outside the current approved indications. Fatal and non-fatal thrombotic events have been reported. Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive NovoSeven RT. Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis. **See WARNINGS AND PRECAUTIONS section of prescribing information.**

Safety and efficacy of NovoSeven RT has not been established outside the approved indications.

1 INDICATIONS AND USAGE

NovoSeven RT Coagulation Factor VIIa (Recombinant) Room Temperature Stable is indicated for:

- 1.1 Treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX and in patients with acquired hemophilia
- 1.2 Prevention of bleeding in surgical interventions or invasive procedures in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX and in patients with acquired hemophilia
- 1.3 Treatment of bleeding episodes in patients with congenital FVII deficiency
- 1.4 Prevention of bleeding in surgical interventions or invasive procedures in patients with congenital FVII deficiency

2 DOSAGE AND ADMINISTRATION

2.1 General

- NovoSeven RT is intended for intravenous bolus administration only.
- Evaluation of hemostasis should be used to determine the effectiveness of NovoSeven RT and to provide a basis for modification of the NovoSeven RT treatment schedule.
- Coagulation parameters do not necessarily correlate with or predict the effectiveness of NovoSeven RT.
- NovoSeven RT should be administered to patients only under the supervision of a physician experienced in the treatment of bleeding disorders.

2.2 Hemophilia A or B with Inhibitors

Treatment of Acute Bleeding Episodes

Hemostatic Dosing

- 90 micrograms/kg given every two hours by bolus infusion until hemostasis is achieved, or until the treatment has been judged to be inadequate.
- Doses between 35 and 120 micrograms/kg have been used successfully in clinical trials for hemophilia A or B patients with inhibitors, and both the dose and administration interval may be adjusted based on the severity of the bleeding and degree of hemostasis achieved.¹
- The minimum effective dose has not been established. For patients treated for joint or muscle bleeds, a decision on outcome was reached for a majority of patients within eight doses although more doses were required for severe bleeds.
- A majority of patients who reported adverse experiences received more than twelve doses.

Post-hemostatic Dosing

- The appropriate duration of post-hemostatic dosing has not been studied.
- For severe bleeds, dosing should continue at 3-6 hour intervals after hemostasis is achieved, to maintain the hemostatic plug.
- The biological and clinical effects of prolonged elevated levels of Factor VIIa have not been studied; therefore, the duration of post-hemostatic dosing should be minimized.
- Patients should be appropriately monitored by a physician experienced in the treatment of hemophilia during this time period.

Dosing for Surgical Interventions

Minor Surgery

- An initial dose of 90 micrograms per kg body weight should be given immediately before the intervention and repeated at 2-hour intervals for the duration of the surgery.
- For minor surgery, post-surgical dosing by bolus injection should occur at 2-hour

intervals for the first 48 hours and then at 2- to 6-hour intervals until healing has occurred.

Major Surgery

- An initial dose of 90 micrograms per kg body weight should be given immediately before the intervention and repeated at 2-hour intervals for the duration of the surgery.
- For major surgery, post-surgical dosing by bolus injection should occur at 2 hour intervals for 5 days, followed by 4 hour intervals until healing has occurred. Additional bolus doses should be administered if required.

2.3 Congenital Factor VII deficiency

The recommended dose range for treatment of bleeding episodes or for prevention of bleeding in surgical interventions or invasive procedures in congenital Factor VII deficient patients is 15-30 micrograms per kg body weight every 4-6 hours until hemostasis is achieved.

- 1 Effective treatment has been achieved with doses as low as 10 micrograms/kg.
- 2 Dose and frequency of injections should be adjusted to each individual.
- 3 The minimum effective dose has not been determined.

2.4 Acquired Hemophilia

- The recommended dose range for the treatment of patients with acquired hemophilia is 70-90 micrograms/kg repeated every 2-3 hours until hemostasis is achieved.
- The minimum effective dose in acquired hemophilia has not been determined.
- The majority of the effective outcomes were observed with treatment in the recommended dose range. The largest number of treatments with any single dose was 90 micrograms/kg; of the 15 treated, 10 (67%) were effective and 2 (13%) were partially effective.

2.5 Reconstitution

Calculate the NovoSeven RT dosage you will need and select the appropriate NovoSeven RT vial package. The selected package contains 1 vial of NovoSeven RT powder and 1 vial of histidine diluent required to prepare reconstituted NovoSeven RT solution. Reconstitute only with the histidine diluent provided with NovoSeven RT. Do not reconstitute with sterile water or other diluent.

Reconstitution should be performed using the following procedures:

1. Always use aseptic technique.
2. Bring NovoSeven RT (white, lyophilized powder) and

the specified volume of histidine (diluent) to room temperature, but not above 37° C (98.6° F). The specified volume of diluent corresponding to the amount of NovoSeven RT is as follows:

1 mg (1000 micrograms) vial + 1.1 mL

Histidine diluent

2 mg (2000 micrograms) vial + 2.1 mL

Histidine diluent

5 mg (5000 micrograms) vial + 5.2 mL

Histidine diluent

8 mg (8000 micrograms) vial + 8.1 mL

Histidine diluent

After reconstitution with the specified volume of diluent, each vial contains approximately 1 mg/mL NovoSeven RT (1000 micrograms/mL).

3. Remove caps from the NovoSeven RT vials to expose the central portion of the rubber stopper. Cleanse the rubber stoppers with an alcohol swab and allow to dry prior to use.
4. Draw back the plunger of a sterile syringe (attached to sterile needle) and admit air into the syringe. It is recommended to use syringe needles of gauge size 20-26.
5. Insert the needle of the syringe into the Histidine diluent vial. Inject air into the vial and withdraw the quantity required for reconstitution.
6. Insert the syringe needle containing the diluent into the NovoSeven RT vial through the center of the rubber stopper, aiming the needle against the side so that the stream of liquid runs down the vial wall (the NovoSeven RT vial does not contain a vacuum). **Do not inject the diluent directly on the NovoSeven RT powder.**
7. Gently swirl the vial until all the material is dissolved. The reconstituted solution is a clear, colorless solution which may be stored either at room temperature or refrigerated for up to 3 hours after reconstitution.

2.6 Administration

- NovoSeven RT is intended for intravenous bolus injection only and should not be mixed with infusion solutions.
- Reconstituted NovoSeven RT should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if particulate matter or discoloration is observed.
- Administration should take place within 3 hours after reconstitution.

- Any unused solution should be discarded. Do not freeze reconstituted NovoSeven RT or store it in syringes.

Administration should be performed using the following procedures:

1. Always use aseptic technique.
2. Draw back the plunger of a sterile syringe (attached to sterile needle) and admit air into the syringe.
3. Insert needle into the vial of reconstituted NovoSeven RT. Inject air into the vial and then withdraw the appropriate amount of reconstituted NovoSeven RT into the syringe.
4. Remove and discard the needle from the syringe.
5. Administer as a slow bolus injection over 2 to 5 minutes, depending on the dose administered.
6. If line needs to be flushed before or after NovoSeven RT administration, use 0.9% Sodium Chloride Injection, USP.
7. Discard any unused reconstituted NovoSeven RT after 3 hours.

3 DOSAGE FORMS AND STRENGTHS

NovoSeven RT is supplied as a white lyophilized powder in single-use vials containing 1 mg (1000 micrograms), 2 mg (2000 micrograms), 5 mg (5000 micrograms), or 8 mg (8000 micrograms) rFVIIa per vial. The diluent for reconstitution of NovoSeven RT is a 10 mmol solution of L-histidine in water for injection and is supplied as a clear colorless solution and is referred to as the histidine diluent. After reconstitution with the histidine diluent, each vial contains approximately 1 mg/mL NovoSeven RT (1000 micrograms/mL).

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Thrombotic Events within the Licensed Indications

Clinical trials within the approved indications revealed that thrombotic events of possible or probable relationship to NovoSeven occurred in 0.28% of bleeding episodes treated, with the incidence within hemophilia patients with inhibitors to be 0.20%, and in acquired hemophilia an incidence of 4%. Thrombotic events have been identified through postmarketing surveillance following NovoSeven RT use for each of the approved indications². The incidence of thrombotic events can not be determined from postmarketing data. Patients with disseminated

intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with aPCCs/PCCs (activated or nonactivated prothrombin complex concentrates) have an increased risk of developing thrombotic events due to circulating tissue factor (TF) or predisposing coagulopathy [See *Adverse Reactions (6.1) and Drug Interactions (7.1)*]. Caution should be exercised when administering NovoSeven RT to patients with an increased risk of thromboembolic complications. These include, but are not limited to, patients with a history of coronary heart disease, liver disease, disseminated intravascular coagulation, post-operative immobilization, elderly patients and neonates. In each of these situations, the potential benefit of treatment with NovoSeven RT should be weighed against the risk of these complications.

Patients who receive NovoSeven RT should be monitored for development of signs or symptoms of activation of the coagulation system or thrombosis. When there is laboratory confirmation of intravascular coagulation or presence of clinical thrombosis, the NovoSeven RT dosage should be reduced or the treatment stopped, depending on the patient's symptoms.

5.2 Thrombotic Events outside the Licensed Indications

NovoSeven has been studied in placebo controlled trials outside the approved indications to control bleeding in intracerebral hemorrhage, advanced liver disease, trauma, cardiac surgery, spinal surgery, and other therapeutic areas. Safety and effectiveness has not been established in these settings and the use is not approved by FDA. Two meta analyses of these pooled data indicate an increased risk of thrombotic events (10.0% in patients treated with NovoSeven versus 7.5% in placebo-treated patients). Arterial thromboembolic adverse events including myocardial infarction, myocardial ischemia, cerebral infarction and cerebral ischemia were statistically significantly increased with the use of NovoSeven compared to placebo (5.3 to 5.6% in subjects treated with NovoSeven versus 2.8 to 3.0% in placebo-treated patients). Other arterial thromboembolic events (such as retinal artery embolism, renal artery thrombosis, arterial thrombosis of limb, bowel infarction and intestinal infarction) have also been reported.^{3,4,5,6,7} While venous thromboembolic events such as deep venous thrombosis, portal vein thrombosis and pulmonary embolism have been reported in clinical trials, the meta analysis of these pooled data from placebo-controlled trials performed outside the currently approved indications did not suggest an increased risk of venous thromboembolic events in patients treated with NovoSeven versus placebo

(4.8% in patients treated with NovoSeven versus 4.7% in placebo-treated patients).

In spontaneous reports of women without a prior diagnosis of bleeding disorders receiving NovoSeven for uncontrolled post-partum hemorrhage, thrombotic events were observed. During this period, patients are at increased risk for thrombotic complications.

5.3 Post-Hemostatic Dosing

Precautions should be exercised when NovoSeven RT is used for prolonged dosing [*See Dosage and Administration (2.2)*].

5.4 Antibody Formation in Factor VII Deficient Patients

Factor VII deficient patients should be monitored for prothrombin time (PT) and factor VII coagulant activity before and after administration of NovoSeven RT. If the factor VIIa activity fails to reach the expected level, or prothrombin time is not corrected, or bleeding is not controlled after treatment with the recommended doses, antibody formation may be suspected and analysis for antibodies should be performed.

5.5 Hypersensitivity Reactions

NovoSeven RT should be administered with caution in patients with known hypersensitivity to NovoSeven RT or any of its components, or in patients with known hypersensitivity to mouse, hamster, or bovine proteins.

5.6 Laboratory Tests

Laboratory coagulation parameters (PT/INR, aPTT, FVII:C) have shown no direct correlation to achieving hemostasis. Assays of prothrombin time (PT/INR), activated partial thromboplastin time (aPTT), and plasma FVII clotting activity (FVII:C), may give different results with different reagents. Treatment with NovoSeven has been shown to produce the following characteristics:

PT: As shown below, in patients with hemophilia A/B with inhibitors, the PT shortened to about a 7second plateau at a FVII:C level of approximately 5 U/mL. For FVII:C levels > 5 U/mL, there is no further change in PT. The clinical relevance of prothrombin time shortening following NovoSeven RT administration is unknown.

<< OLE Object: Microsoft Word Picture >>

FVII:C (U/mL)

INR: NovoSeven has demonstrated the ability to normalize INR. However, INR values have not been shown to directly predict bleeding outcomes, nor has it been possible to demonstrate the impact of NovoSeven on bleeding times/volume in models of clinically-induced bleeding in healthy volunteers who had received Warfarin, when laboratory parameters (PT/INR, aPTT, thromboelastogram) have normalized.

aPTT: While administration of NovoSeven shortens the prolonged aPTT in hemophilia A/B patients with inhibitors, normalization has usually not been observed in doses shown to induce clinical improvement. Data indicate that clinical improvement was associated with a shortening of aPTT of 15 to 20 seconds.

FVIIa:C: FVIIa:C levels were measured two hours after NovoSeven administration of 35 micrograms/kg and 90 micrograms/kg following two days of dosing at two hour intervals. Average steady state levels were 11 and 28 U/mL for the two dose levels, respectively.

6 ADVERSE REACTIONS

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug product cannot be directly compared to rates in clinical trials of another drug, and may not reflect rates observed in practice.

6.1 Clinical Trials Experience

Thrombotic events following the administration of NovoSeven occurred in 0.28% of bleeding episodes treated, with the incidence in acquired hemophilia of 4% and in hemophilia patients of 0.20% in clinical trials within the approved indications [*See Warnings and Precautions (5.1)*].

Adverse reactions observed in clinical trials for all labeled indications of NovoSeven included pyrexia, hemorrhage, injection site reaction, arthralgia, headache, hypertension, hypotension, nausea, vomiting, pain, edema, rash (including allergic dermatitis and rash erythematous), pruritus, urticaria, hypersensitivity, cerebral artery occlusion, cerebrovascular accident, pulmonary embolism, deep vein thrombosis, angina pectoris, increased levels of fibrin degradation products, disseminated intravascular

coagulation and related laboratory findings including elevated levels of D-dimer and AT-III, thrombosis at i.v. site, non-specified thrombosis, thrombophlebitis, superficial thrombophlebitis.

The following sections describe the adverse event profile observed during clinical studies for each of the labeled indications.

Hemophilia A or B Patients with Inhibitors

Two studies (Studies 1 and 2) are described for hemophilia A or B patients with inhibitors treated for bleeding episodes [See *Clinical Studies (14.1)*]. The table below lists adverse events that were reported in 32% of the 298 patients with hemophilia A or B with inhibitors that were treated with NovoSeven for 1,939 bleeding episodes. The events listed are considered to be at least possibly related or of unknown relationship to NovoSeven administration.

Body System	# of episodes reported	# of unique patients
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Event (n=1,939 treatments) (n=298 patients)

Body as a whole

Fever	16	13
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Platelets, Bleeding, and Clotting

Hemorrhage NOS	15	8
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Fibrinogen plasma decreased	10	5
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Skin and Musculoskeletal

Hemarthrosis	14	8
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Cardiovascular

Hypertension	9	6
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Events which were reported in 1% of patients and were considered to be at least possibly or of unknown relationship to NovoSeven administration were: allergic reaction, arthrosis, bradycardia, coagulation disorder, DIC, edema, fibrinolysis increased, headache, hypotension, injection site reaction, pain, pneumonia, prothrombin decreased, pruritus, purpura, rash, renal function abnormal, therapeutic response decreased, and vomiting.

Serious adverse events that were probably or possibly related, or where the relationship to NovoSeven was not specified, occurred in 14 of the 298 patients (4.7%). Six of the 14 patients died of the following conditions: worsening of chronic renal failure, anesthesia complications during proctoscopy, renal failure complicating a retroperitoneal bleed, ruptured abscess leading to sepsis and DIC, pneumonia, and splenic hematoma and gastrointestinal bleeding. Thrombosis was reported in two of the 298 patients with hemophilia.

Surgery Studies

Two clinical trials (Studies 3 and 4) were conducted to evaluate the safety and efficacy of NovoSeven administration during and after surgery in hemophilia A or B patients with

inhibitors [See *Clinical Studies (14.1)*].

In Study 3, six patients experienced serious adverse events: two of these patients had events which were considered probably or possibly related to study medication (acute post-operative hemarthrosis, internal jugular thrombosis). No deaths occurred during the study.

In Study 4, seven of 24 patients had serious adverse events (4 for bolus injection, 3 for continuous infusion). There were 4 serious adverse events which were considered probably or possibly related to NovoSeven treatment (2 events of decreased therapeutic response in each treatment arm). No deaths occurred during the study period.

Congenital Factor VII Deficiency

Data collected from the compassionate/emergency use programs, the published literature, a pharmacokinetics study, and the Hemophilia and Thrombosis Research Society (HTRS) registry showed that at least 75 patients with Factor VII deficiency had received NovoSeven - 70 patients for 124 bleeding episodes, surgeries, or prophylaxis regimens; 5 patients in the pharmacokinetics trial.

In the compassionate/emergency use programs, 28 adverse events in 13 patients and 10 serious adverse events in 9 patients were reported. Non-serious adverse events in the compassionate/emergency use programs were single events in one patient, except for fever (3 patients), intracranial hemorrhage (3 patients), and pain (2 patients). The most common serious adverse event in the compassionate/emergency programs was serious bleeding in critically ill patients. All nine patients with serious adverse events died. One adverse event (localized phlebitis) was reported in the literature. No adverse events were reported in the pharmacokinetics reports or for the HTRS registry. No thromboembolic complications were reported for the 75 patients included here.

As with all therapeutic proteins, there is a potential for immunogenicity. Isolated cases of factor VII deficient patients developing antibodies against factor VII were reported after treatment with NovoSeven. These patients had previously been treated with human plasma and/or plasma-derived factor VII. In some cases the antibodies showed inhibitory effect *in vitro*. The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection,

concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to NovoSeven RT with the incidence of antibodies to other products may be misleading.

Acquired Hemophilia

Data collected from four compassionate use programs, the HTRS registry, and the published literature showed that 139 patients with acquired hemophilia received NovoSeven for 204 bleeding episodes, surgeries and traumatic injuries.

Of these 139 patients, 10 experienced 12 serious adverse events that were of possible, probable, or unknown relationship to treatment with NovoSeven. Thrombotic serious adverse events included cerebral infarction, cerebral ischemia, angina pectoris, myocardial infarction, pulmonary embolism and deep vein thrombosis. Additional serious adverse events included shock and subdural hematoma.

Data collected for mortality in the compassionate use programs, the HTRS registry and the publications spanning a 10 year period, was overall 32/139 (23%). Deaths due to hemorrhage were 10, cardiovascular failure 4, neoplasia 4, unknown causes 4, respiratory failure 3, thrombotic events 2, sepsis 2, arrhythmia 2 and trauma 1.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of NovoSeven. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship.

The following additional adverse events were reported following the use of NovoSeven in labeled and unlabeled indications that included individuals with and without coagulopathy: high D-dimer levels and consumptive coagulopathy, thrombosis, thrombophlebitis, arterial thrombosis, and thromboembolic events including myocardial ischemia, myocardial infarction, bowel infarction, cerebral ischemia, cerebral infarction, hepatic artery thrombosis, renal artery thrombosis, portal vein thrombosis, phlebitis, peripheral ischemia, deep vein thrombosis and related pulmonary embolism, injection site pain and isolated cases of hypersensitivity/allergic reactions including anaphylactic shock, flushing, urticaria, rash, and angioedema [*See Warnings and Precautions (5.1)*].

Fatal and non-fatal thromboembolic events have been reported with use of NovoSeven when used for off-label or

labeled indications.

The Hemophilia and Thrombosis Research Society (HTRS) Registry surveillance program is designed to collect data on the treatment of congenital and acquired bleeding disorders.⁸ All prescribers can obtain information regarding contribution of patient data to this program by calling [1-877-362-7355](tel:1-877-362-7355) or at www.novosevensurveillance.com.

7 DRUG INTERACTIONS

7.1 Coagulation Factor Concentrates

The risk of a potential interaction between NovoSeven RT and coagulation factor concentrates has not been adequately evaluated in preclinical or clinical studies. Simultaneous use of activated prothrombin complex concentrates or prothrombin complex concentrates should be avoided.

7.2 Infusion Solutions

NovoSeven RT should not be mixed with infusion solutions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. NovoSeven RT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Treatment of rats and rabbits with NovoSeven in reproduction studies has been associated with mortality at doses up to 6 mg/kg and 5 mg/kg. At 6 mg/kg in rats, the abortion rate was 0 out of 25 litters; in rabbits at 5 mg/kg, the abortion rate was 2 out of 25 litters. Twenty-three out of 25 female rats given 6 mg/kg of NovoSeven gave birth successfully, however, two of the 23 litters died during the early period of lactation. No evidence of teratogenicity was observed after dosing with NovoSeven.

8.2 Labor and Delivery

NovoSeven was administered to a FVII deficient patient (25 years of age, 66 kg) during a vaginal delivery (36 micrograms/kg) and during a tubal ligation (90 micrograms/kg). No adverse reactions were reported during labor, vaginal delivery, or the tubal ligation.

There are no adequate and well-controlled studies in labor, delivery, and postpartum periods. In spontaneous reports of women without a prior diagnosis of bleeding disorders receiving NovoSeven for uncontrolled post-partum hemorrhage, thrombotic events were observed. During this period, patients are at increased risk for thrombotic complications. It is not known to what extent NovoSeven contributed to the occurrence of these events.

8.3 Nursing Mothers

It is not known whether NovoSeven RT is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Clinical trials enrolling pediatric patients were conducted with dosing determined according to body weight and not according to age. The safety and effectiveness of NovoSeven RT has not been studied to determine if there are differences among various age groups, from infants to adolescents (0 to 16 years of age).

8.5 Geriatric Use

Clinical studies of NovoSeven in congenital factor deficiencies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

10 OVERDOSAGE

There are no adequate and well controlled studies to support the safety or efficacy of using higher than labeled doses in the indicated populations.

Dose limiting toxicities of NovoSeven RT have not been investigated in clinical trials. The following are examples of accidental overdose.

Congenital Factor VII Deficiency

A newborn female with congenital factor VII deficiency was administered an overdose of NovoSeven (single dose: 800 micrograms/kg). Following additional administration of NovoSeven and various plasma products, antibodies against rFVIIa were detected, but no thrombotic complications were reported. A Factor VII deficient male (83 years of age, 111.1 kg) received two doses of 324 micrograms/kg (10-20 times the recommended

dose) and experienced a thrombotic event (occipital stroke).

Hemophilia A or B with Inhibitors

One hemophilia B patient (16 years of age, 68 kg) received a single dose of 352 micrograms/kg and one hemophilia A patient (2 years of age, 14.6 kg) received doses ranging from 246 micrograms/kg to 986 micrograms/kg on five consecutive days. There were no reported complications in either case.

11 DESCRIPTION

NovoSeven RT is recombinant human coagulation Factor VIIa (rFVIIa), intended for promoting hemostasis by activating the extrinsic pathway of the coagulation cascade.⁹ NovoSeven RT is a vitamin K dependent glycoprotein consisting of 406 amino acid residues (MW 50 K Dalton). NovoSeven RT is structurally similar to human plasmaderived Factor VIIa.

The gene for human Factor VII is cloned and expressed in baby hamster kidney cells (BHK cells). Recombinant FVII is secreted into the culture media (containing newborn calf serum) in its single-chain form and then proteolytically converted by autocatalysis to the active two-chain form, rFVIIa, during a chromatographic purification process. The purification process has been demonstrated to remove exogenous viruses (MuLV, SV40, Pox virus, Reovirus, BEV, IBR virus). No human serum or other proteins are used in the production or formulation of NovoSeven RT.

NovoSeven RT is supplied as a sterile, white lyophilized powder of rFVIIa in singleuse vials. Each vial of lyophilized drug contains the following:

Contents	1 mg Vial	2 mg Vial	5 mg Vial	8 mg Vial
rFVIIa	1000 micrograms	2000 micrograms	5000 micrograms	8000 micrograms
sodium chloride*	2.34 mg	4.68 mg	11.7 mg	18.72 mg
calcium chloride dihydrate*	1.47 mg	2.94 mg	7.35 mg	11.76 mg
glycylglycine	1.32 mg	2.64 mg	6.60 mg	10.56 mg
polysorbate 80	0.07 mg	0.14 mg	0.35 mg	0.56 mg
mannitol	25 mg	50 mg	125 mg	200 mg
Sucrose	10 mg	20 mg	50 mg	80 mg
Methionine	0.5 mg	1.0 mg	2.5 mg	4 mg

* per mg of rFVIIa: 0.4 mEq sodium, 0.01 mEq calcium

The diluent for reconstitution of NovoSeven RT is a 10 mmol solution of histidine in water for injection and is supplied as a clear colorless solution.

After reconstitution with the appropriate volume of **histidine** diluent, each vial contains approximately 1 mg/mL NovoSeven RT (corresponding to 1000 micrograms/mL). The reconstituted vials have a pH of approximately 6.0 in sodium chloride (2.3 mg/mL), calcium chloride dihydrate (1.5 mg/mL), glycylglycine (1.3 mg/mL), polysorbate 80 (0.1 mg/mL), mannitol (25 mg/mL), sucrose (10 mg/mL), methionine (0.5 mg/mL), and

histidine (1.6 mg/mL).

The reconstituted product is a clear colorless solution which contains no preservatives. NovoSeven RT contains trace amounts of proteins derived from the manufacturing and purification processes such as mouse IgG (maximum of 1.2 ng/mg), bovine IgG (maximum of 30 ng/mg), and protein from BHK-cells and media (maximum of 19 ng/mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

NovoSeven RT is recombinant Factor VIIa and, when complexed with tissue factor can activate coagulation Factor X to Factor Xa, as well as coagulation Factor IX to Factor IXa. Factor Xa, in complex with other factors, then converts prothrombin to thrombin, which leads to the formation of a hemostatic plug by converting fibrinogen to fibrin and thereby inducing local hemostasis. This process may also occur on the surface of activated platelets.

12.2 Pharmacodynamics

The effect of NovoSeven RT upon coagulation in patients with or without hemophilia has been assessed in different model systems. In an *in vitro* model of tissue-factor-initiated blood coagulation (Figure A)¹⁰, the addition of rFVIIa increased both the rate and level of thrombin generation in normal and hemophilia A blood, with an effect shown at rFVIIa concentrations as low as 10 nM. In this model, fresh human blood was treated with corn trypsin inhibitor (CTI) to block the contact pathway of blood coagulation. Tissue factor (TF) was added to initiate clotting in the presence and absence of rFVIIa for both types of blood.

In a separate model, and in line with previous reports¹¹, escalating doses of rFVIIa in hemophilia plasma demonstrate a dose-dependent increase in thrombin generation (Figure B). In this model, platelet rich normal and hemophilia plasma was adjusted with autologous plasma to 200,000 platelets/microliter. Coagulation was initiated by addition of tissue factor and CaCl₂. Thrombin generation was measured in the presence of a thrombin substrate and various added concentrations of rFVIIa.

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TF-initiated clotting of normal blood and congenital hemophilia A blood in the presence of factor VIIa. Clotting of CTI-inhibited (0.1 mg/mL) normal blood initiated with 12.5 pM TF (<< OLE Object: Picture (Metafile) >>) and addition of 10 nM factor

VIIa (<< OLE Object: Picture (Metafile) >>) and of hemophilia A blood with (<< OLE Object: Picture (Metafile) >>) and without (<< OLE Object: Picture (Metafile) >>) addition of 10 nM factor VIIa. Figure A shows Thrombin Anti-Thrombin generation over time. Arrows indicate clotting times.

Figure B

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TF-initiated clotting of normal and hemophilia A platelet rich plasma in the presence of rFVIIa.

12.3 Pharmacokinetics

Healthy Subjects

The pharmacokinetics of NovoSeven was investigated in 35 healthy Caucasian and Japanese subjects in a dose-escalation study. Subjects were stratified according to gender and ethnic group and dosed with 40, 80 and 160 micrograms/kg NovoSeven.¹² The pharmacokinetics of rFVII were linear over the dose range of 40 to 180 micrograms/kg. Pharmacokinetics were similar across gender and ethnic groups. Mean steady state volume of distribution ranged from 130 to 165 mL/kg, mean values of clearance ranged from 33 to 37 mL/h x kg, and mean terminal half-life ranged from 3.9 to 6.0 hours.

Hemophilia A or B

Single-dose pharmacokinetics of NovoSeven (17.5, 35, and 70 micrograms/kg) exhibited dose-proportional behavior in 15 subjects with hemophilia A or B.¹³ Factor VII clotting activities were measured in plasma drawn prior to and during a 24-hour period after NovoSeven administration. The median apparent volume of distribution at steady state was 103 mL/kg (range 78-139). Median clearance was 33 mL/kg/hr (range 27-49). The median residence time was 3.0 hours (range 2.4-3.3), and the $t_{1/2}$ was 2.3 hours (range 1.7-2.7). The median *in vivo* plasma recovery was 44% (30-71%). The products NovoSeven RT and NovoSeven are pharmacokinetically equivalent.¹⁴

In a bolus single-dose pharmacokinetic study, 5 male adults (90 micrograms/kg) and 10 male pediatric (2-12 years) patients (crossover, 90 and 180 micrograms/kg) with severe hemophilia A (10 of 18 subjects had inhibitors) received NovoSeven.¹⁵ The PK of rFVII following 90 and 180 micrograms/kg IV dose in children indicated dose linearity. Based on the FVII:C assay, the terminal half-life of NovoSeven was 2.6 hrs in pediatric patients and 3.1 hrs in adults. Based on the 90 microgram/kg dose, the total clearance of NovoSeven in adults and children was 2767 ± 385 mL/hr (37.6 ± 13.1 mL/hr/kg) and 1375 ± 396 mL/hr (57.3 ± 9.5 mL/hr/kg), respectively. The volume of

distribution at steady state (V_{ss}) in adults and children was 121 ± 30 and 153 ± 29 mL/kg, respectively.

Congenital Factor VII deficiency

Single dose pharmacokinetics of NovoSeven in congenital Factor VII deficiency, at doses of 15 and 30 micrograms per kg body weight, showed no significant difference between the two doses used with regard to dose-independent parameters: total body clearance (70.8-79.1 mL/hr x kg), volume of distribution at steady state (280-290 mL/kg), mean residence time (3.75-3.80 hr), and half-life (2.82-3.11 hr). The mean *in vivo* plasma recovery was approximately 20% (18.9%-22.2%).

The normal Factor VII plasma concentration is 0.5 micrograms/mL. Factor VII levels of 15-25% (0.075 – 0.125 micrograms/mL) are generally sufficient to achieve normal hemostasis.¹⁶ For example, a 70 kg individual with FVII deficiency (plasma volume of approximately 3000 mL) would thus require 3.2 - 5.4 micrograms/kg of NovoSeven RT to secure hemostasis, assuming 100% recovery but, since the mean plasma recovery for NovoSeven is 20% for FVII-deficient patients, a NovoSeven RT dose range of 16-27 micrograms/kg would be required to achieve sufficient FVII plasma levels for hemostasis, which is consistent with the recommended dose range.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two mutagenicity studies have given no indication of carcinogenic potential for NovoSeven. The clastogenic activity of NovoSeven was evaluated in both *in vitro* studies (*i.e.*, cultured human lymphocytes) and *in vivo* studies (*i.e.*, mouse micronucleus test). Neither of these studies indicated clastogenic activity of NovoSeven. Other gene mutation studies have not been performed with NovoSeven RT (*e.g.*, Ames test). No chronic carcinogenicity studies have been performed with NovoSeven RT.

A reproductive study in male and female rats at dose levels up to 3.0 mg/kg/day had no effect on mating performance, fertility, or litter characteristics.

Treatment of rats and rabbits with NovoSeven in reproduction studies has been associated with mortality at doses up to 6 mg/kg and 5 mg/kg. At 6 mg/kg in rats, the abortion rate was 0 out of 25 litters; in rabbits at 5 mg/kg,

the abortion rate was 2 out of 25 litters. Twenty-three out of 25 female rats given 6 mg/kg of NovoSeven gave birth successfully, however, two of the 23 litters died during the early period of lactation. No evidence of teratogenicity was observed after dosing with NovoSeven.

14 CLINICAL STUDIES

No direct comparisons to other coagulation products have been conducted, therefore no conclusions regarding the comparative safety or efficacy can be made.

14.1 Hemophilia A or B with Inhibitors

Open Protocol Use

The largest number of patients who received NovoSeven during the investigational phase of product development were in an open protocol study (Study 1)^{17,18,19} that began enrollment in 1988, shortly after the completion of the pharmacokinetic study. These patients included persons with hemophilia types A or B (with or without inhibitors), persons with acquired inhibitors to Factor VIII or Factor IX, and a few FVII deficient patients. The clinical situations were diverse and included muscle/joint bleeds, mucocutaneous bleeds, surgical prophylaxis, intracerebral bleeds, and other emergent situations. Dose schedules were suggested by Novo Nordisk, but they were subject to the option of the investigator. Clinical outcomes were not reported in a standardized manner. Therefore, the clinical data from Study 1 are problematic for the evaluation of the safety and efficacy of the product by statistical methods.

Dosing Study

Study 2²⁰ was a double-blind, randomized comparison trial of two dose levels of NovoSeven in the treatment of joint, muscle and mucocutaneous hemorrhages in hemophilia A and B patients with and without inhibitors. Patients received NovoSeven as soon as they could be evaluated in the treatment centers (4 to 18 hours after experiencing a bleed). Thirty-five patients were treated at the 35 micrograms/kg dose (59 joint, 15 muscle and 5 mucocutaneous bleeding episodes) and 43 patients were treated at the 70 micrograms/kg dose (85 joint and 14 muscle bleeding episodes).

Dosing was to be repeated at 2.5 hour intervals but ranged up to four hours for some patients. Efficacy was assessed at 12 ± 2 hours or at end of treatment, whichever occurred first. Based on a subjective evaluation by the investigator, the respective efficacy rates for the 35 and 70

micrograms/kg groups were: excellent 59% and 60%, effective 12% and 11%, and partially effective 17% and 20%. The average number of injections required to achieve hemostasis was 2.8 and 3.2 for the 35 and 70 micrograms/kg groups, respectively.

One patient in the 35 micrograms/kg group and three in the 70 micrograms/kg group experienced serious adverse events that were not considered related to NovoSeven. Two unrelated deaths occurred; one patient died of AIDS and the other of intracranial hemorrhage secondary to trauma.

Surgery Studies

Two clinical trials (Studies 3 and 4) were conducted to evaluate the safety and efficacy of NovoSeven administration during and after surgery in hemophilia A or B patients with inhibitors.

Study 3 was a randomized, double-blind, parallel group clinical trial (29 patients with hemophilia A or B and inhibitors or acquired inhibitors to FVIII/FIX, undergoing major or minor surgical procedures).²¹ Patients received bolus intravenous NovoSeven (either 35 micrograms/kg, N=15; or 90 micrograms/kg, N=14) prior to surgery, intra-operatively as required, then every 2 hours for the following 48 hours beginning at closure of the wound. Additional doses were administered every 2 to 6 hours up to an additional 3 days to maintain hemostasis. After a maximum of 5 days of double-blind treatment, therapy could be continued in an open-label manner if necessary (90 micrograms/kg NovoSeven every 2-6 hours). Efficacy was assessed during the intra-operative period, and post-operatively from the time of wound closure (Hour 0) through Day 5.

When efficacy assessments at each time point were tabulated by a last value carried forward approach (patients who completed the study early having achieved effective hemostasis were counted as "effective" and those who discontinued due to treatment failure or adverse events were counted as "ineffective" at each time point thereafter), the results at the end of the 5-day double-blind treatment period were as summarized in the table below. Twenty-three patients successfully completed the entire study (including the open-label period after the 5-day double blind period) with satisfactory hemostasis.

Study 3: Dose Comparison of Efficacy in Major and Minor Surgery - Last Value Carried Forward*

Number of effective (E)/ineffective (I) responses in each dose group

**Major Surgery
35 mg/kg****

Minor Surgery

(n = 5) **90 mg/kg**

(n = 6) **35 mg/kg**

(n = 10) **90 mg/kg**

(n = 8) **Total**

		(n = 29)													
		Major Surgery 35 mg/kg**			Minor Surgery 90 mg/kg						Minor Surgery 35 mg/kg			Total	
		E	I		E	I	E	I	E	I	E	I	E	I	
Intraoperative			5	0		6	0		10	0		7	1		
Post-Op Hour		0		5	0		6	0		8	2		6		
	8	4	1		5	1		9	1		7	1			
	24	4	1		6	0		9	1		6	2			
	48	3	2		6	0		8	2		8	0			
Day	3	2	3		6	0		8	2		8	0			
	4	3	2		6	0		8	2		8	0			
	5	3	2		5	1		8	2		8	0			

* Patients who completed the study early having achieved effective hemostasis were counted as effective at subsequent time-points, and patients who discontinued due to treatment failure or adverse events were counted as ineffective at subsequent time-points. Only effective ratings were counted as successful hemostasis (ratings of "partially effective" were not counted). Ten patients completed the study by Day 5 because their bleeding had resolved and they were discharged from the hospital. Three patients dropped out of the study due to ineffective therapy and 1 patient left the study due to an adverse event.

** µg/kg = micrograms/kg

E: Number of patients where NovoSeven treatment was effective; I: Number of patients where NovoSeven treatment was ineffective

Study 3: Dosing by Surgery Category

**Major Surgery
35 mg/kg***

Minor Surgery

(n = 5) **90 mg/kg**

	(n = 6)	35 mg/kg	
	(n = 10)	90 mg/kg	
Days of dosing, median (range)	(n = 8) 15 (2-26)	9.5 (8-17)	4 (3-6)
No. injections, median (range)	6 (3-13) 135 (11-186)	81 (71-128)	29.5
Median total dose, mg (range)	(24-44) 656 (31-839)	39.5 (26-98) 569 (107-698)	45.5
	(14-171) 67 (31-122)		
	* µg/kg = micrograms/kg		

Study 4 was an open-label, randomized, parallel trial conducted to compare the safety and efficacy of IV bolus (N=12) and IV continuous infusion (N=12) administration of NovoSeven in hemophilia A or B patients with inhibitors who were undergoing elective major surgery. The types of surgeries that were performed included knee (N=13), hip (N=3), abdomen/lower pelvis (N=2), groin/inguinal area (N=2), circumcision (N=1), eye (N=1), frontal/temporal region of cranium (N=1), and oral cavity (N=1).

Prior to surgery, a 90 micrograms/kg bolus dose of NovoSeven was administered to both bolus and continuous infusion groups. The bolus injection group then received 90 micrograms/kg NovoSeven by IV bolus injection every 2 hours during the procedure and for the first 5 days, then every 4 hours from Day 6 to Day 10. The continuous infusion group received 50 micrograms/kg/h NovoSeven by IV continuous infusion for the first 5 days, and infusion of 25 micrograms/kg/h from Day 6 to Day 10. For both NovoSeven-treated groups, two bolus rescue doses of 90 micrograms/kg were permitted during any 24-hour period.

The bolus injection (90 micrograms/kg) and continuous infusion (50 micrograms/kg/h) treatment groups showed comparable efficacy in achieving and maintaining hemostasis in major surgery from wound closure through Day 10. For the Global Hemostasis Treatment Evaluation for overall success in achieving and maintaining hemostasis at the end of the study period, treatment was rated as being effective in 9 patients (75%) and ineffective in 3 patients (25%) for both treatment groups.

When efficacy assessments at each time point were tabulated by a last value carried forward approach (patients who completed the study early having achieved effective hemostasis were counted as "effective" at each time point, and those who discontinued due to treatment failure counted as "ineffective" at each time point thereafter), the results were as summarized in the table below.

Study 4: Efficacy of Bolus Dosing vs. Continuous

Infusion in Major Surgery - Last Value Carried Forward*

**Number of effective (E)/ineffective (I) responses in each dose group
Bolus Injection**

(NovoSeven 90 micrograms/kg)

n = 12 **Continuous Infusion**

(NovoSeven 50 micrograms/kg/h)

		n = 12			
		E		I	
		Post-Op			
Hour	0	12	0	12	0
	8	12	0	11	1
	24	12	0	10	2
	48	10	2	11	1
	72	9	3	11	1
Day	4	11	1	10	2
	5	11	1	10	2
	6	11	1	10	2
	7	9	3	10	2
	8	10	2	10	2
	9	9	3	10	2
	10	9	3	10	2

* Patients who completed the study early having achieved hemostasis counted as effective at subsequent time-points, and patients who discontinued due to treatment failure counted as ineffective at subsequent time-points. Eight patients completed the study early because their bleeding had resolved and they were discharged from the hospital. Four patients dropped out of the study due to ineffective therapy and 1 patient left the study due to a hemarthrosis that was described as an adverse event.

E: Number of patients where NovoSeven treatment was effective; I: Number of patients where NovoSeven treatment was ineffective

Study 4: Dosing by Treatment Group

**Bolus Injection Continuous Infusion
90 micrograms/kg**

(n = 12) **50 micrograms/kg/h**

		(n = 12)	
Days of dosing, median (range)		10 (4-15) ^a	10 (2-116)
No. bolus injections,			
median (range)	38 (36-42)	1.5 (0-7)	

No. of additional bolus injections, median (range)

0 (0-3)

0 (0-4)

Mean total dose, mg

237.5

292.2

^a Includes dosing during the follow-up period after the 10-day study period.

14.2 Congenital Factor VII Deficiency

Data were collected from the published literature and internal sources for 70 patients with Factor VII deficiency treated with NovoSeven for 124 bleeding episodes, surgeries, or prophylaxis regimens. Thirty-two of these patients were enrolled in emergency and compassionate use trials conducted by Novo Nordisk (43 non-surgical bleeding episodes, 26 surgeries); 35 were reported in the published literature (20 surgeries, 10 non-surgical bleeding episodes, 4 cases of caesarean section or vaginal birth, and 10 cases of long-term prophylaxis, and 1 case of on-demand therapy); and 3 were from a registry maintained by the Hemophilia and Thrombosis Research Society (9 bleeding episodes, 1 surgery). Dosing ranged from 6-98 micrograms/kg administered every 2-12 hours (except for prophylaxis, where doses were administered from 2 times per day up to 2 times per week). Patients were treated with an average of 1-10 doses. Treatment was effective (bleeding stopped or treatment was rated as effective by the physician) in 93% of episodes (90% for trial patients, 98% for published patients, 90% for HTRS registry patients).

14.3 Acquired Hemophilia

Data were collected from four studies in the compassionate use program conducted by Novo Nordisk and the Hemophilia and Thrombosis Research Society (HTRS) registry. A total of 70 patients with acquired hemophilia were treated with NovoSeven for 113 bleeding episodes, surgeries, or traumatic injuries. Sixty-one of these patients were from the compassionate use program with 100 bleeding episodes (68 non-surgical and 32 surgical bleeding episodes) and 9 patients were from the HTRS registry with 13 bleeding episodes (8 non-surgical, 3 surgical and 2 episodes classified as other). Concomitant use of other hemostatic agents

occurred in 29/70 (41%); 13 (19%) received more than one hemostatic agent. The most common hemostatic agents used were antifibrinolytics, Factor VIII and activated prothrombin complex concentrates.

The compassionate use programs and the HTRS registry were not designed to select doses or compare first-line efficacy or efficacy when used after failure of other hemostatic agents (salvage treatment). A dose response was not seen in doses ranging from 70-90 micrograms/kg.

The mean dose of NovoSeven administered was 90 micrograms/kg (range: 31 to 197 micrograms/kg); the mean number of injections per day was 6 (range: 1 to 10 injections per day). Overall efficacy i.e., effective and partially effective outcomes, was 87/112 (78%); with 77/100 (77%) efficacy in the compassionate use programs and 10/12 (83%) efficacy in the HTRS registry. In the compassionate use programs, overall efficacy for the first-line treatment was 38/44 (86%) compared to 39/56 (70%) when used as salvage treatment.

Efficacy by Dose Group, for Patients Receiving Doses Ranging from <61 to >90 micrograms/kg NovoSeven, Compassionate Use Programs and HTRS Registry

Outcome ^a	NovoSeven Dose (micrograms/kg)										Total
	Un-known	<61	61-69	70-80	81-89	90	>90				
Effective N (%)	1 (33)	3 (75)	5 (63)	10 (63)	12 (57)	10 (67)	26 (58)	67			
Partial N (%)	1 (33)	0 (0)	0 (0)	3 (19)	3 (14)	2 (13)	11 (24)	20			
Ineffective N (%)	0 (0)	1 (25)	3 (38)	2 (13)	2 (10)	2 (13)	7 (16)	17			
Unknown N (%)	1 (33)	0 (0)	0 (0)	1 (6)	4 (19)	1 (7)	1 (2)	8			
No. of Bleeding Episodes^c		3	4	8	16	21	15	45	112 ^b		

^a Outcome assessed at end of treatment, last observation carried forward.

^b One patient in the HTRS registry was excluded from efficacy analysis since NovoSeven was used to maintain hemostasis after bleeding had been controlled.

^c N (%) do not add up to 100 due to rounding.

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16 HOW SUPPLIED/STORAGE AND HANDLING

NovoSeven RT Coagulation Factor VIIa (Recombinant) Room Temperature Stable is supplied as a white, lyophilized powder in singleuse vials, one vial per carton. The vials are made of glass, closed with a latex-free, chlorobutyl rubber stopper, and sealed with an aluminum cap. The vials are equipped with a snapoff polypropylene cap. The amount of rFVIIa in milligrams and in micrograms is stated on the label as follows:

1 mg per vial (1000 micrograms/vial) NDC 0169-7010-01

2 mg per vial (2000 micrograms/vial) NDC 0169-7020-01

5 mg per vial (5000 micrograms/vial) NDC 0169-7050-01

8 mg per vial (8000 micrograms/vial) NDC 0169-7040-01

The diluent for reconstitution of NovoSeven RT is a 10 mmol solution of L-histidine in water for injection and is supplied as a clear colorless solution, and referred to as the histidine diluent. The vials are made of glass closed with a latex-free, chlorobutyl rubber disc, and covered with an aluminum cap. The closed vials are equipped with a tamper-evident snap-off cap which is made of polypropylene.

Prior to reconstitution, keep refrigerated or store between 2-25°C/36-77°F. Do not freeze. Store protected from light. Do not use past the expiration

date.

After reconstitution, NovoSeven RT may be stored either at room temperature or refrigerated for up to 3 hours. Do not freeze reconstituted NovoSeven RT or store it in syringes.

17 PATIENT COUNSELING INFORMATION

Patients receiving NovoSeven RT should be informed of the benefits and risks associated with treatment. Patients should be warned about the early signs of hypersensitivity reactions, including hives, urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. Patients should also be warned about the signs of thrombosis, including new onset swelling and pain in the limbs or abdomen, new onset chest pain, shortness of breath, loss of sensation or motor power, or altered consciousness or speech. Patients should be told to immediately seek medical help if any of the above signs or symptoms occur.

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