

PRODUCT MONOGRAPH

Schedule D

NovoMix[®] 30

(30% soluble insulin aspart, 70% insulin aspart protamine crystals)

Solution for Injection

100 Units/mL

Professed

Antidiabetic Agent

Novo Nordisk Canada Inc.
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NovoMix® 30

(30% soluble insulin aspart, 70% insulin aspart protamine crystals)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous injection.	Suspension for injection, 100 Units/mL	glycerol, phenol, metacresol, zinc (as chloride), sodium chloride, disodium hydrogen phosphate dihydrate, protamine sulphate, sodium hydroxide, hydrochloric acid, water for injections. <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

DESCRIPTION

NovoMix® 30 (30% soluble insulin aspart and 70% insulin aspart protamine crystals) is a dual release human insulin analogue suspension containing 30% soluble insulin aspart and 70% insulin aspart protamine crystals.

NovoMix® 30 has rapid absorption characteristics. The soluble insulin aspart in NovoMix® 30 is absorbed rapidly from the subcutaneous layer. The remaining is in crystalline form as insulin aspart protamine which has prolonged absorption after subcutaneous injection.

INDICATIONS AND CLINICAL USE

NovoMix® 30 is indicated for the treatment of adult patients with diabetes mellitus who require insulin for the control of hyperglycemia.

Geriatrics (>65 years of age):

Clinical studies of NovoMix 30 did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients.

Pediatric (<16 years of age):

No adequate data are available to establish the effectiveness in pediatrics.

CONTRAINDICATIONS

NovoMix[®] 30 is contraindicated:

- During episodes of hypoglycemia
- In patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the *Dosage Forms, Composition and Packaging* section of the product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

NovoMix[®] 30 should be given immediately before or after a meal because of the fast onset of action (start of the meal should be not more than 5-10 minutes after injection) (see **Recommended Dose and Dosage Adjustment**).

Insulin aspart differs from regular human insulin by its rapid onset and shorter duration of action. Because of the fast onset of action, the injection of **NovoMix[®] 30** should immediately be followed by a meal. To avoid possible transmission of disease, a Penfill[®] cartridge or FlexPen[®] prefilled insulin syringe must not be used by more than one person.

When patients are transferred between different types of insulin products, the early warning symptoms of hypoglycemia may change or become less pronounced than those experienced with their previous insulin

General

Transferring a patient to a new type or brand of insulin should be done under strict medical supervision. Changes in strength, brand, type, species (animal, human, human insulin analogue), and/or method of manufacture may result in the need for a change in dosage.

Transfer to NovoMix[®] 30 from other insulin preparations may require adjustment of dose and timing of administration. If an adjustment is needed, it may be done with the first dose or during the first few weeks or months.

As with all insulins, the duration of action of NovoMix[®] 30 may vary in different individuals or in the same individual according to dose, injection site, blood flow, temperature and level of physical activity.

Hypokalemia is among the potential clinical adverse effects associated with the use of all insulins. This potential clinical adverse effect may be relevant in patients who are on potassium lowering drugs.

Stress or illness may change insulin requirements. In these instances, patients should contact their physician and carefully control their blood glucose.

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

Concomitant illness, especially infections, usually increases the patient's insulin requirements.

Carcinogenesis and Mutagenesis

See *PART II: Scientific Information – Toxicology*.

Endocrine and Metabolism

Hypoglycemia

In certain cases (long duration of diabetes, diabetic nerve disease, intensified diabetes control, or use of medications such as beta blocking agents), the nature and intensity of early warning symptoms of hypoglycemia may change or be less pronounced

Hypoglycemia is the most frequently occurring undesirable effect of insulin therapy. Such reactions following treatment with NovoMix[®] 30, are mostly mild and easily managed.

Severe hypoglycemia can result in temporary or permanent impairment of brain function and death.

Changes in insulin therapy or changes in life style (i.e. diet, exercise/physical activity) may require a change in dosage. Inadequate dosing or discontinuation of insulin treatment, especially in Type 1 diabetes, may lead to hyperglycemia and diabetic ketoacidosis. Severe sustained hyperglycemia may result in diabetic coma and death.

Glucose monitoring is recommended for all patients with diabetes.

The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may constitute a risk in situations where these abilities are of special importance (e.g., driving a car or operating machinery).

Hepatic/Biliary/Pancreas

There is no experience of treatment with insulin aspart in patients with hepatic impairment. As with other insulins, **NovoMix[®] 30** requirement may need to be adjusted in patients with hepatic impairment (see *Action and Clinical Pharmacology - Pharmacokinetics*).

Immune

Antibody production: Insulin antibodies may develop during treatment with insulin. Insulin antibody production was monitored during the clinical development program for NovoMix[®] 30. A transitory 11.2% increase in cross-reactive antibodies observed during the initial 3 months of treatment with NovoMix[®] 30 in the phase III trial was followed by a significant decrease from month 3 to 12. This decrease was maintained between months 12 and 24, where concentrations were constant at about 5 absolute percentage points above baseline for the Type 2 diabetic subjects and 7.02% for the total population (Type 1 and 2 diabetic subjects). No relationship between cross-reactive antibody level and metabolic control, insulin dose requirements or adverse events has been observed.

Local Allergic Reaction: As with other insulins, 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. They may occur if the injection is not properly made, or if the patient is allergic to the insulin or any excipients. Few local injection site reactions were observed with NovoMix[®] 30 in the clinical development program and there was no difference in frequency when compared to human insulin.

Systemic Allergic Reaction: Systemic allergic reactions have not been reported during the clinical development of NovoMix[®] 30. Systemic allergic reactions have rarely occurred with NovoMix[®] 30 as with other insulin treatment. These reactions may be characterized by a generalized rash (with pruritus), shortness of breath, wheezing and drop in blood pressure. Severe cases of generalized allergy including anaphylactic reaction may be life threatening.

Renal

There is no experience of treatment with insulin aspart in patients with renal impairment. As with other insulins, NovoMix[®] 30 requirement may be reduced in patients with renal impairment.

Sexual Function/Reproduction

There is no information on teratogenicity of insulin aspart in humans. In rabbit trials, insulin aspart did not exert any direct adverse effect on fertility, mating performance, reproductive capacity or embryo-fetal development and did not differ from human insulin.

Special Populations

Pregnant Women: There are no clinical studies of the use of NovoMix[®] 30 in pregnancy. Animal reproduction studies have not revealed any differences between insulin aspart and human insulin regarding embryotoxicity or teratogenicity. In general, intensified blood glucose control and monitoring of pregnant women with diabetes are recommended throughout pregnancy and when contemplating pregnancy. Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimesters. After delivery, insulin requirements return rapidly to pre-pregnancy levels.

Nursing Women: There are no clinical studies of the use of **NovoMix[®] 30** in nursing women. It is unknown whether NovoMix[®] 30 is excreted in significant amounts in human milk. For this reason, caution should be exercised when NovoMix[®] 30 is administered to a nursing mother. Patients with diabetes who are lactating may require adjustments in insulin dose, meal plan or both.

Pediatrics (< 16 years of age): The safety and effectiveness of NovoMix[®] 30 have not been established in children. (**See PART II: Scientific Information – Clinical Trials**).

Geriatrics:

The effect of age on the pharmacokinetics and pharmacodynamics of NovoMix[®] 30 has not been studied.

Monitoring and Laboratory Tests

As with all insulin therapy the need for regular blood glucose self-monitoring should be considered when using NovoMix[®] 30 to obtain optimal glycemic control. Careful monitoring of the patient is required throughout pregnancy. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse drug reactions observed with NovoMix[®] 30 are mainly dose-dependent and due to the pharmacologic effect of insulin. As for other insulin products, hypoglycemia, in general is the most frequently occurring undesirable effect. It may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

NovoMix[®] 30 has been evaluated for safety in patients with type 1 and type 2 diabetes in a open-label, parallel-group trial of 24 month duration (067/D/UK). A total of 204 patients were exposed to a twice daily regimen of treatment of NovoMix[®] 30 (n=101) and Biphasic Human Insulin 30 (n = 103).

Table 1 - Distribution of the most common Adverse Events occurring in >1% of patients with Type 1 or Type 2 Diabetes from 24 month study for NovoMix®.

	NovoMix® 30		BHI 30	
	N	(%)	N	(%)
Number of Subjects Exposed	101		103	
Adverse Events				
Respiratory System Disorders				
Upper Respiratory tract infection	46	46%	35	34%
Pharyngitis	16	16%	10	10%
Coughing	12	12%	8	8%
Rhinitis	10	10%	9	9%
Sinusitis	5	5%	3	3%
Bronchitis	4	4%	3	3%
Dyspnoea	2	2%	3	3%
Pneumonia			2	2%
Pulmonary Oedema			2	2%
Chronic obstructive airways disease			2	2%
Central & Peripheral Nervous System Disorders				
	29	29%	17	17%
Headache	10	10%	12	12%
Sensory disturbance	9	9%	9	9%
Hyporeflexia	8	8%	8	8%
Neuropathy	3	3%	4	4%
Migraine	3	3%	2	2%
Cramps legs	2	2%	3	3%
Dizziness	2	2%	1	<1%
Vertigo	1	<1%	3	3%
Neuralgia				
Body as a Whole - General Disorders				
Influenza-like symptoms	21	21%	20	19%
Back pain	11	11%	5	5%
Leg pain	5	5%	4	4%
Allergic Reaction	4	4%	3	3%
Headache	4	4%	1	<1%
Fatigue	2	2%	2	2%
Allergy	2	2%	1	<1%
Pain	2	2%	1	<1%
Malaise	2	2%		
Nasal polyp	2	2%		
Chest pain	1	<1%	5	5%

	NovoMix® 30		BHI 30	
	N	(%)	N	(%)
Carpal tunnel syndrome			2	2%
Gastro-Intestinal System Disorders				
Dyspepsia	13	13%	9	9%
Diarrhea	12	12%	13	13%
Abdominal pain	8	8%	5	5%
Tooth ache	6	6%	4	4%
Nausea	5	5%	7	7%
Gastroenteritis	4	4%	1	<1%
Vomiting	3	3%	9	9%
Constipation	3	3%	4	4%
Gingivitis	2	2%	2	2%
Tooth disorder	2	2%	2	2%
Oesophagitis	2	2%		
Gastritis			4	4%
Gastro-intestinal disorder nos			2	2%
Musculo-Skeletal System Disorders				
Arthralgia	9	9%	6	6%
Skeletal pain	8	8%	7	7%
Back pain	7	7%	3	3%
Myalgia	7	7%	1	<1%
Arthropathy	3	3%	3	3%
Arthritis	2	2%	3	3%
Arthrosis	2	2%	2	2%
Bone disorder	2	2%	1	<1%
Ischias			3	3%
Resistance Mechanism Disorders				
Infection	15	15%	17	17%
Infection fungal	4	4%	4	4%
Moniliasis	3	3%	4	4%
Infection viral	2	2%	2	2%
Abscess	2	2%	1	<1%
Herpes simplex	2	2%		
Infection wound	1	<1%	3	3%
Upper respiratory tract infection	1	<1%	2	2%
Skin and Appendages Disorders				
Skin disorder	5	5%	4	4%
Rash	4	4%	4	4%
Skin ulceration	3	3%	4	4%
Eczema	3	3%	3	3%

	NovoMix® 30		BHI 30	
	N	(%)	N	(%)
Dermatitis fungal	3	3%		
Urticaria	3	3%		
Hyperkeratosis	2	2%	1	<1%
Seborrhoea	2	2%	1	<1%
Skin dry	2	2%	1	<1%
Pruritus	1	<1%	2	2%
Metabolic and Nutritional Disorders				
Hypercholesterolaemia	7	7%	2	2%
Hyperlipaemia	4	4%	5	5%
Lipid metabolism disorder nos	3	3%		
Diabetes mellitus aggravated	2	2%		
Gout	2	2%		
Weight decrease	2	2%		
Hyperglycaemia	1	<1%	3	3%
Hypoglycemia	1	<1%	2	2%
Oedema leg				2%
Cardiovascular Disorders, General				
Hypertension	16	16%	14	14%
Cardiac Failure	3	3%	3	3%
Heart Murmur	1	<1%	2	2%
Oedema Dependent			2	2%
Secondary Terms				
Injury accidental	12	12%	15	15%
Vision Disorders				
Retinal disorder	5	5%	4	4%
Conjunctivitis	2	2%	1	<1%
Retinal hemorrhage	2	2%	1	<1%
Vision abnormal	2	2%	1	<1%
Eye abnormality			3	3%
Urinary System Disorders				
Urinary tract infection	5	5%	9	9%
Cystitis	2	2%	2	2%
Albuminuria	2	2%	1	<1%
Haematuria			3	3%
Renal function abnormal			2	2%
Liver and Biliary System Disorders				
Hepatic enzymes increased	4	4%		

	NovoMix® 30		BHI 30	
	N	(%)	N	(%)
Cholecystitis			2	2%
Psychiatric Disorders				
Depression	3	3%	3	3%
Anxiety	2	2%	4	4%
Impotence	2	2%		
Vascular (extra cardiac) disorders				
Peripheral ischaemia	3	3%	1	<1%
Vascular disorder	1	<1%	3	3%
Myo Endo Pericardial & Valve Disorders				
Myocardial ischaemia	4	4%		
Angina pectoris	2	2%	3	3%
Coronary artery disorder	1	<1%	2	2%
Myocardial infarction			2	2%
Neoplasm				
Pulmonary carcinoma	2	2%		
Application Site Disorders				
Fibrous nodule	2	2%		
Reproductive Disorders, Female				
Dysmenorrhoea	2	2%	2	2%
Heart Rate and Rhythm Disorders				
Arrhythmia	2	2%	1	<1%
Red Blood Cell Disorders				
Erythrocytes abnormal	2	2%		
Anaemia Secondary Terms			3	3%
Injury accidental				
Hearing and Vestibular Disorders				
Earache	2	2%	2	2%

N = Number of subjects with event

% = Proportion of exposed subjects having the event

BHI 30 = Biphasic Human Insulin 30

Less Common Clinical Trial Adverse Drug Reactions (<1%) Reported in patients with Type 1 or Type 2 Diabetes

Eye disorders:

Uncommon (>1/1,000, <1/100): Refraction Disorder

Refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

Uncommon (>1/1000, <1/100): Diabetic Retinopathy

Long-term improved glycemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycemic control may be associated with worsening of diabetic retinopathy.

General Disorders:

Uncommon (>1/1,000, <1/100): Edema

Edema may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

Immune System Disorders:

Uncommon (>1/1000, <1/100): Urticaria, rash, eruptions

Very rare (<1/10 000): Anaphylactic responses

Symptoms of generalised hypersensitivity may include generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation and reduction in blood pressure. Generalised hypersensitivity reactions are potentially life threatening.

Nervous System Disorders:

Rare (>1/10,000, <1/1000): Peripheral neuropathy

Fast improvement in blood glucose control may be associated with a condition termed acute painful neuropathy, which is usually reversible.

Skin and subcutaneous tissue disorder:

Uncommon (>1/1000, <1/100): Local hypersensitivity

Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.

Uncommon (>1/1000, <1/100): Lipodystrophy

Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

Post-Market Adverse Drug Reactions [*Guidance for Industry – Product Monograph, 2004 – Appendix I – Product Monograph Template Schedule D – 3 Aug 2007 Clarifax, Control No. 110755*]

Based on post-marketing experience with NovoMix® 30, Serious adverse reactions reported during the post-marketing period, include:

- Hypersensitivity and injection site reactions such as erythema, swelling, rash, pruritus and injection site mass. Local hypersensitivity reactions may occur during treatment with insulin. (Rare $>1/10,000$ and $\leq 1/1,000$).
- Anti-insulin antibodies. Human insulin is known to be antigenic with low titres of antibodies developing in most patients (up to 80%). The effect of insulin antibodies on insulin pharmacokinetics, with the presence of binding IgG in serum, may delay time to peak levels of free insulin. Antibodies may be cross-reactive to both insulin aspart and human insulin. No correlation to lack of efficacy or safety concerns has been identified in connection with these reports. (Very rare $\leq 1/10,000$).
- Hyperglycaemia and diabetic ketoacidosis. Inadequate dosing or discontinuation of treatment may, especially in type 1 diabetes, lead to hyperglycemia. Untreated hyperglycemia may lead to ketoacidosis. Concomitant illness, especially infections, usually increases the patients' insulin requirements, thus patients should always be informed to increase their insulin dose in case of fever and/or other infections. (Rare $>1/10,000$ and $\leq 1/1,000$).
- Hypoglycemia including hypoglycemic coma. As for other insulin products, hypoglycemia, in general is the most frequent occurring undesirable effect. Special attention should always be paid during dose intensification. (Very rare $\leq 1/10,000$).
- Very few anaphylactic reactions including anaphylactic shock have been reported. Patients with a history of allergic reactions should be carefully monitored. (Very rare $\leq 1/10,000$).
- Dyspnoea. Very few cases have been reported on Dyspnoea. In the vast majority of the cases dyspnoea is reported in connection with hypersensitivity or allergic reactions. (Very rare $\leq 1/10,000$).

DRUG INTERACTIONS

Serious Drug Interactions

NovoMix[®] 30 should not be mixed with any other insulin products.

Overview

A number of medicinal products are known to interact with glucose metabolism. Therefore, concomitant use of other drugs with **NovoMix[®] 30** may influence insulin requirements. See *Drug-Drug Interactions* below.

Drug - Drug Interactions

The following substances may reduce the insulin requirements: oral antidiabetic agents, monoamine oxidase inhibitors (MAOI), non-selective beta adrenergic blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, alcohol, anabolic steroids and sulphonamides.

Other drugs may increase insulin requirements: oral contraceptives, thiazides, glucocorticosteroids, thyroid hormones, sympathomimetics, growth hormone and danazol.

Octreotide/lanreotide may both increase and decrease insulin requirements.

Beta blocking agents may mask the symptoms of hypoglycemia.

Alcohol may intensify and prolong the hypoglycemic effect of insulin.

Drug-Food Interactions

Please refer to *Dosage and Administration - Recommended Dose and Dosage Adjustment and Warnings and Precautions* regarding the timing of food consumption and NovoMix[®] 30 administration.

Drug-Herb Interactions

Interactions with herbal products have not been investigated.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been investigated.

Drug-Lifestyle Interactions

The effect of smoking on the pharmacokinetics and pharmacodynamics of NovoMix[®] 30 have not been studied. Patients should be informed about the potential advantages and disadvantages of NovoMix[®] 30 therapy including the possible side effects. Patients should also be offered continued education and advice on insulin therapies, life-style management, self-monitoring, complications of insulin therapy, timing of dosage, instruction for use of injection devices and storage of insulin.

The need for regular blood glucose self-monitoring should be considered when using NovoMix[®] 30 to obtain optimal glycemic control.

Female patients should be advised to discuss with their physician if they intend to or if they become pregnant.

DOSAGE AND ADMINISTRATION

Dosing Considerations

NovoMix[®] 30 should be given immediately before or after a meal because of the fast onset of action (start of the meal should be not more than 5-10 minutes after injection). When necessary, NovoMix[®] 30 may be given immediately after the meal.

New Patients:

Patients can be initiated on NovoMix[®] 30 in the same manner as they would be on animal-source or human premix insulin.

Transfer Patients:

When patients are transferred from other insulin to NovoMix[®] 30, the change should be made as directed by the physician.

In clinical trials, of NovoMix[®] 30, patients were transferred on a unit to unit basis from human premixed 30/70 or human NPH to NovoMix[®] 30 with doses subsequently adjusted according to individual needs.

Recommended Dose and Dosage Adjustment

Dosage of NovoMix[®] 30 is individual and determined, based on the physician's advice, in accordance with the needs of the patient. The individual insulin requirement is usually between 0.5 - 1.0 units/kg/day. In a premixed insulin regimen, the total daily dose can be provided by NovoMix[®] 30 immediately before meals.

Administration

NovoMix[®] 30 is administered subcutaneously in the abdominal wall, the thigh, the upper

arm or the buttock. Care should be taken to avoid entry into a blood vessel. Injection sites should be rotated within the same region. As with all insulin, the duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

NovoMix[®] 30 is a white suspension. The carton contains a package leaflet with instructions for use and handling. The necessity of properly re-suspending NovoMix[®] 30 immediately before use should be stressed to the patient. The re-suspended liquid must appear uniformly white and cloudy. NovoMix[®] 30 should not be used after its expiration date. NovoMix[®] 30 should not be injected intravenously.

In patients with diabetes mellitus, optimized metabolic control effectively delays the onset and slows the progression of late diabetic complications. Optimized metabolic control, including glucose monitoring is therefore recommended.

OVERDOSAGE

Overdose may cause hypoglycemia. Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia. Symptoms of hypoglycemia may occur suddenly. They may include cold sweat, cool pale skin, fatigue, nervousness or tremor, anxious feeling, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may be fatal.

Mild episodes of hypoglycemia can be treated by oral administration of glucose or sugary products. It is therefore recommended that patients with diabetes always carry some sugar candy.

Severe hypoglycemic episodes, where the patient has become unconscious, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person or glucose given intravenously by a medical professional. Glucose must also be given intravenously if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of an oral carbohydrate is recommended for the patient in order to prevent relapse.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The primary activity of NovoMix[®] 30 is the regulation of glucose metabolism. Insulins, including NovoMix[®] 30, 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.

Pharmacodynamics

The pharmacodynamic response to a single dose of 0.3U/kg NovoMix® 30 and premixed human insulin 30/70 was investigated in 24 healthy subjects using the hyperinsulinaemic euglycemic clamp method* (Trial ANA-033). NovoMix® 30 shows a significantly greater metabolic effect in the first 4 hours after subcutaneous injection than the premixed human insulin 30/70 (see Figure 1).

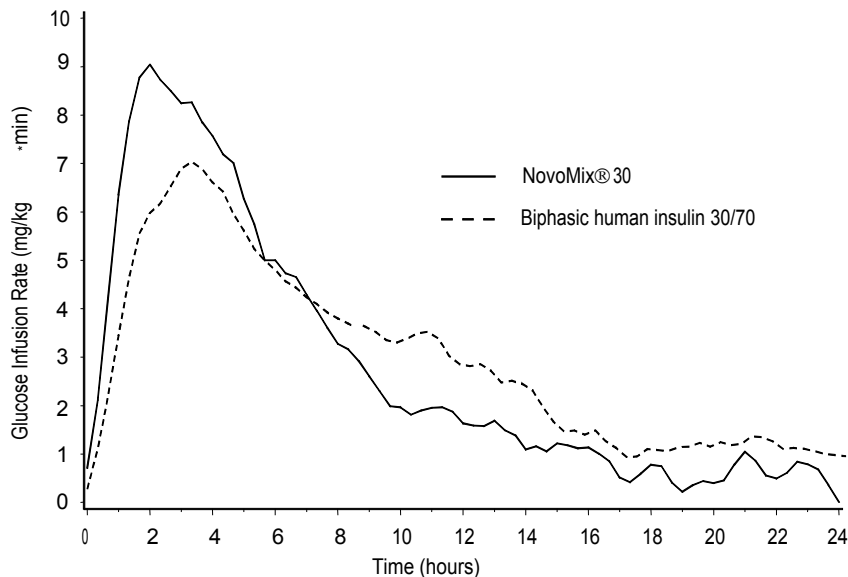


Figure 1: Pharmacodynamic activity profile of NovoMix® 30 and biphasic human insulin 30/70 in healthy subjects (ANA-033)

In a randomized, double-blind, two-way cross-over trial ANA-046 comparing NovoMix® 30 and biphasic human insulin 30/70 in patients with Type 2 diabetes, the therapeutic response was evaluated following two 2-week treatment periods where insulin was administered in a twice daily dose regimen; immediately before breakfast and dinner. The shape of the 24-hour total serum glucose concentration-time profiles was different between the treatments over time (see Figure 2 below). Although there was no difference detected between treatments with respect to average serum glucose levels over 24 hours, the estimated mean time-action curves shown below indicate that postprandial glucose control was superior with NovoMix® 30 compared to biphasic human insulin 30/70, following dinner and breakfast but inferior after lunch.

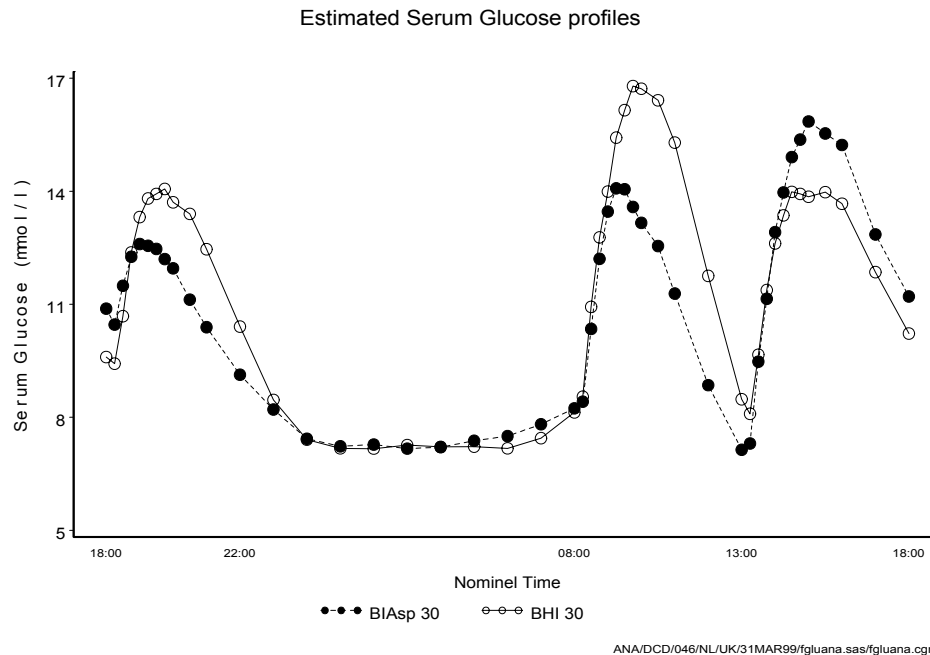


Figure 2: Estimated serum glucose levels following twice daily injection (immediately before breakfast and dinner) of NovoMix[®] 30 (NovoMix[®] 30) or biphasic human insulin (BHI 30) in 13 patients with Type 2 diabetes (ANA-046).

In clinical trial NovoMix[®] -1235, 61 subjects with Type 2 diabetes received a single dose of NovoMix[®] 30, Humalog[®] Mix25 and Novolin[®] ge 30/70 (insulin, human biosynthetic) on three separate occasions in a cross-over trial. Postprandial glycaemic control, as assessed by the 5-hour post meal serum glucose excursion was statistically significantly improved (a 10% reduction, $p < 0.05$) with NovoMix[®] 30 over Humalog[®] Mix25 and Novolin[®] ge 30/70 (a 17% reduction, $p < 0.001$).⁸ For NovoMix[®] 30 versus Novolin[®] ge 30/70, maximum glucose concentration was reduced and occurred earlier. Compared to Humalog[®] Mix25 there was a shorter time to maximum glucose concentration.

NovoMix[®] 30 is a dual-release insulin analogue suspension containing 30% soluble insulin aspart. This soluble fraction has a rapid onset of action while the crystalline phase (70%) which consists of insulin aspart protamine, has an activity profile similar to that of human NPH insulin.

The effect of NovoMix[®] 30 is more rapid in onset compared to biphasic human insulin (i.e., human biosynthetic insulin) due to the faster absorption of the soluble component after subcutaneous injection.

When NovoMix[®] 30 is injected subcutaneously, the onset of action will occur within 10 to 20 minutes of injection. The maximum effect is exerted between 1 and 4 hours after injection. The duration of action is up to 24 hours.

Pharmacokinetics

Bioavailability and Absorption of NovoMix® 30

NovoMix® 30 exhibits rapid absorption characteristics. The insulin aspart in the soluble component of NovoMix® 30 is absorbed more rapidly from the subcutaneous layer than regular soluble human insulin. The remaining is in crystalline form as insulin aspart protamine that has a prolonged absorption profile after subcutaneous injection.

The relative bioavailability of NovoMix® 30 compared to premixed human insulin 30/70 indicates that they are absorbed to similar degrees.

The maximum serum insulin concentration (C_{max}) for NovoMix® 30 is, on average, 50% higher than with biphasic human insulin 30/70 (Figure 3). The time to maximum concentration (T_{max}) is, on average, half that for biphasic human insulin 30/70. In healthy volunteers, a mean maximum serum concentration of 23.4 ± 5.3 mU/L was reached about 60 minutes after a subcutaneous dose of 0.2 U/kg body weight versus 15.5 ± 3.7 mU/L at about 130 minutes for biphasic human insulin 30/70. The mean half life ($t_{1/2}$) of NovoMix® 30, reflecting the absorption rate of the protamine bound fraction, was about 8-9 hours. Serum insulin levels returned to baseline about 15-18 hours after a subcutaneous dose. In Type 2 diabetic patients, the maximum concentration was reached about 95 minutes after dosing.

Pharmacokinetic Profiles of NovoMix[®] 30 and biphasic human insulin 30/70

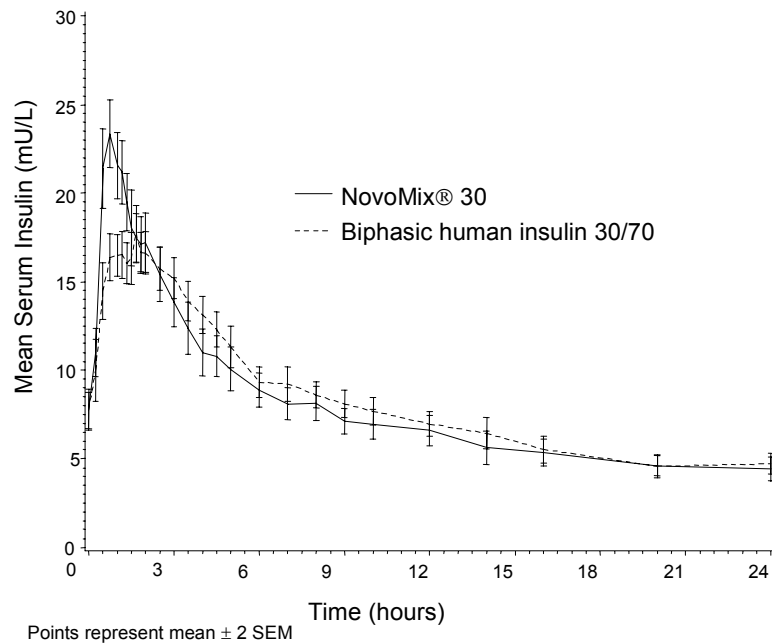


Figure 3: Mean serum insulin concentration following a single subcutaneous dose (0.2U/kg body weight) of NovoMix[®] 30 (solid line) and biphasic human insulin 30/70 (hatched line) in healthy subjects.

Distribution and Elimination:

Insulin aspart has a low binding to plasma proteins, 0-9%. After subcutaneous administration, insulin aspart 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.

Special Populations and Conditions

Pediatrics:

The effect of age on the pharmacokinetics and pharmacodynamics of NovoMix[®] 30 has not been studied.

Geriatrics:

The effect of age on the pharmacokinetics and pharmacodynamics of NovoMix[®] 30 has not been studied.

Gender:

The effect of gender on the pharmacokinetics and pharmacodynamics of NovoMix[®] 30 has not been studied.

Race:

The effect of ethnic origin on the pharmacokinetics and pharmacodynamics of NovoMix[®] 30 has not been studied.

Hepatic Insufficiency:

As with other insulin, NovoMix[®] 30 requirement may need to be adjusted in patients with hepatic impairment.

Renal Insufficiency:

As with other insulin, **NovoMix[®] 30** requirement may be reduced in patients with renal impairment.

Genetic Polymorphism:

No specific information is available.

STORAGE AND STABILITY

NovoMix[®] 30 should be stored between 2 and 10°C. Do not freeze. Cartridges, vials or FlexPen[®] in use or carried as a spare may be kept at room temperature (not above 30°C) for up to 4 weeks, but should not be exposed to excessive heat or sunlight.

NovoMix[®] 30 should not be used after the expiry date printed on the package.

NovoMix[®] 30 which has been frozen must not be used.

SPECIAL HANDLING INSTRUCTIONS

Penfill[®]: The cartridges are designed to be used with Novo Nordisk delivery devices and NovoFine[®] needles.

Detailed instruction accompanying the cartridge and delivery system must be followed.

FlexPen[®]: NovoFine[®] needles are designed to be used with FlexPen[®] detailed instruction accompanying the delivery system must be followed.

NovoMix[®] 30 Penfill[®]/FlexPen[®] is for use by one person only. The cartridge must not be refilled.

The necessity of resuspending the NovoMix[®] 30 suspension immediately before use is to be stressed to the patient. The resuspended liquid must appear uniformly white and cloudy.

The patient should be advised to discard the needle after each injection.

DOSAGE FORMS, COMPOSITION AND PACKAGING

NovoMix[®] 30 is available in 3 mL Penfill[®] cartridges (in cartons of 5 cartridges) and in 3 mL NovoMix[®] 30 FlexPen[®] prefilled pens (in cartons of 1 and 5 pens). All presentations are in strengths of 100 Units of insulin aspart per mL.

The cartridge and glass ball are made of Type 1 glass, colourless, the rubber closure is a laminate disc made of latex-free (isoprene and bromobutyl) rubber, the plunger is made of latex-free (bromobutyl) rubber, and the cap is made of aluminum.

NovoMix[®] 30 Penfill[®] cartridges are designed for use with Novo Nordisk Insulin Delivery Devices and NovoFine[®] needles. NovoMix[®] 30 FlexPen[®] is specially designed for use with NovoFine[®] needles.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Insulin Aspart

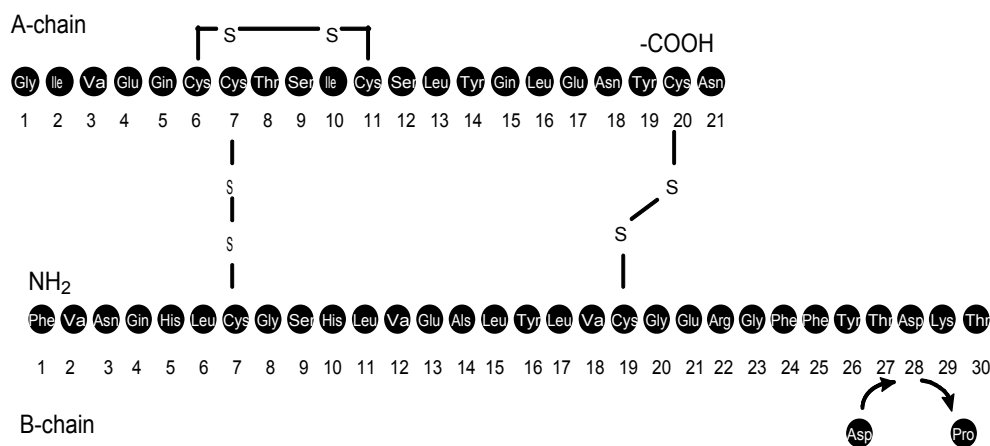
Chemical name: B28 asp regular human insulin analogue

Molecular formula and molecular mass:

$C_{256}H_{381}N_{65}O_{79}S_6$ and 5825.8 g/mole

Insulin aspart is an analogue of human insulin, in which the amino acid proline in position B28 has been replaced by aspartic acid

Figure 1 - Structural formula



Structural formula of insulin aspart

Physicochemical properties:

Description: sterile, uniform, white suspension of soluble insulin aspart and protamine-crystallized insulin aspart.

pH: 7.20-7.44 One unit of insulin aspart corresponds to 6 nmol, 0.035 mg salt-free anhydrous insulin aspart.

Product Characteristics

The manufacture of the drug substance consists of the following three major steps: fermentation, recovery, and purification. In the recovery phase, the fermentation broth undergoes an alkaline treatment and the yeast cells are removed by centrifugation.

CLINICAL TRIALS

In a randomized, double-blind, two-way cross-over trial comparing NovoMix® 30 and biphasic human insulin 30/70 in patients with Type 2 diabetes, the therapeutic response was evaluated following two 2-week treatment periods where insulin was administered in a twice daily dose regimen; immediately before breakfast and dinner. The shape of the 24-hour total serum glucose concentration-time profiles were statistically significantly different between treatments over time (see Figure 2 below). Although there was no difference detected between treatments with respect to average serum glucose levels over 24 hours, the estimated mean time-action curves shown below indicate that postprandial glucose control was superior with NovoMix® 30 compared to biphasic human insulin 30/70, following dinner and breakfast but higher after lunch.

Estimated Mean 24-hour Serum Glucose Profiles

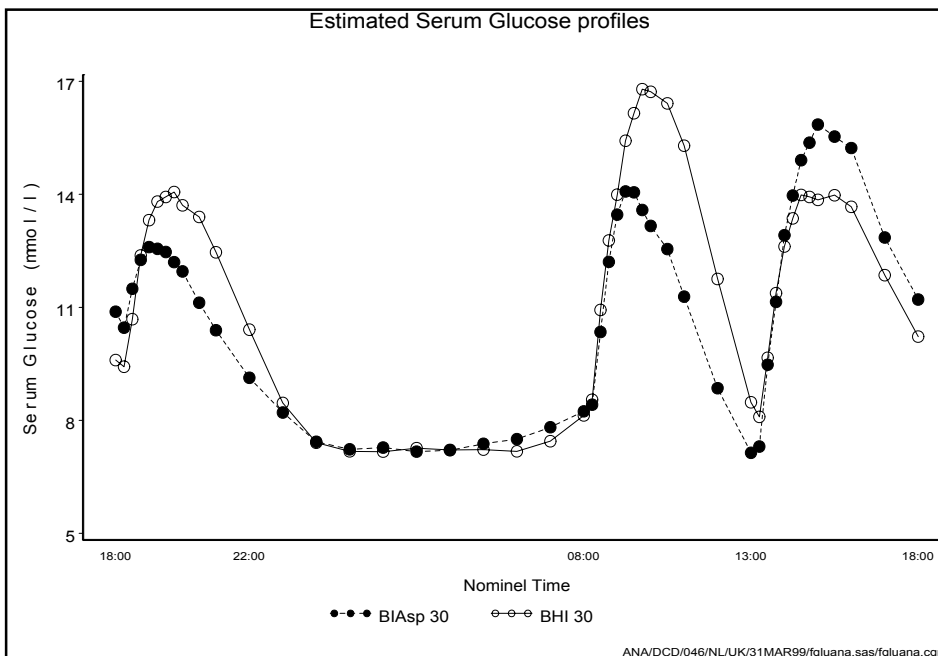


Figure 2: Estimated serum glucose levels following twice daily injection (immediately before breakfast and dinner) of NovoMix® 30 (NovoMix® 30) or biphasic human insulin (BHI 30) in 13 patients with Type 2 diabetes.

In a 3 month, multicentre, open-labelled, randomized, parallel group study, NovoMix® 30 was as effective as biphasic human insulin 30/70 (Novolin®ge 30/70) in long-term glycemic control, based on HbA_{1C} levels. Mealtime blood glucose increment averaged over the three main meals was statistically significantly different (29% lower) in the

NovoMix[®] 30 group ($p < 0.02$) and statistically significant differences (approximately 1 mmol/l lower) were observed in mean blood glucose levels after breakfast, before lunch, after dinner and at bedtime ($p < 0.02-0.05$). Improvements in postprandial glycemic control did not increase the risk of hypoglycemia. Patients wishing to continue in an extension of this study were followed for an additional 21 month period on either NovoMix[®] 30 or Novolin[®]ge 30/70. At the end of the 24 month period of treatment, glycemic control, as measured by HbA_{1c}, was similar in the two groups.

With similar levels of glycemic control (as assessed by HbA_{1c}), the number and rate of hypoglycemic episodes was similar in patients with Type 1 diabetes. However, for patients with Type 2 diabetes, those treated with NovoMix[®] 30 had a lower frequency of major hypoglycemia than those receiving Novolin[®]ge 30/70 and during the last six months of the study, no patients treated with NovoMix[®] 30 experienced major hypoglycemia.

In a clinical trial, 61 subjects with Type 2 diabetes received a single dose of NovoMix[®] 30, Humalog[®] Mix25 and Novolin[®]ge 30/70 (insulin, human biosynthetic) on three separate occasions in a cross-over trial. Postprandial glycemic control, as assessed by the 5-hour post meal serum glucose excursion was statistically significantly improved (a 10% reduction, $p < 0.05$) with NovoMix[®] 30 over Humalog[®] Mix25 and Novolin[®]ge 30/70 (a 17% reduction, $p < 0.001$). For NovoMix[®] 30 versus Novolin[®]ge 30/70, maximum glucose concentration was reduced and occurred earlier. Compared to Humalog[®] Mix25 there was a shorter time to maximum glucose concentration.

One hundred and fifty-one Type 2 patients inadequately treated with oral diabetes medication (metformin with/without insulin secretagogues) were entered into a clinical trial. During the first 4 weeks of the trial, patients were titrated to target with metformin only. Those patients who did not achieve fasting glycemic levels within the target range of 5 - 7 mmol/l ($n = 140$) were initiated on insulin therapy in a randomized fashion to receive one of three insulin treatment regimens once a day in combination with the metformin therapy: NovoMix[®] 30 (at dinner), Novolin[®]ge 30/70 (at dinner) or Novolin[®] NPH (before bed). There were no statistically significant differences between treatment groups for long term glycemic control; mean HbA_{1c} levels were reduced from baseline by 1.1 - 1.3% with 12 weeks of treatment. There was no significant difference in reporting of hypoglycemic events among the three groups although fewer patients reported nocturnal hypoglycemic events in the NovoMix[®] 30 group than in the other groups. At the end of the study, the final fasting plasma glucose fell within target range (5-7 mmol/l) for 9 subjects in the NovoMix[®] 30 group, 9 subjects in the Novolin[®]ge NPH group and 8 subjects in the Novolin[®]ge 30/70 group. The mean decrease in HbA_{1c} values experienced by these subjects (-2.3%, -1.9% and -1.8% respectively) were greater than observed for the total study population.

Metformin-treated patients with Type 2 diabetes ($n = 341$) were randomized to receive NovoMix[®] 30 monotherapy BID, NovoMix[®] 30 BID with existing metformin or sulphonylurea therapy with existing metformin. In the total population, the mean difference in HbA_{1c} levels was statistically significant only for subjects receiving

NovoMix® 30 plus metformin versus NovoMix® 30 monotherapy ($p = 0.004$). Mean decrease in HbA_{1c} during the study was 1.5 - 1.8% in all groups. In 193 patients with poorly controlled diabetes at the start of the trial (HbA_{1c} 9.0%), the mean difference in HbA_{1c} was statistically significant in the NovoMix® 30 plus metformin group versus the NovoMix® 30 monotherapy group ($p = 0.037$) and the sulphonylurea plus metformin group ($p = 0.033$) after 16 weeks of treatment. Mean HbA_{1c} decrease during the study was 1.9 to 2.4% in all groups.

The efficacy and safety of NovoMix® 30 in NovoMix® 30 FlexPen® was compared with Humalog® Mix25 in Humalog® Mix25 Pen in 132 insulin-treated patients with Type 2 diabetes in a open-label, two-period crossover design trial. Following a 2-week run-in period on NovoMix® 30, patients began the first 12-week treatment period on either NovoMix® 30 or Humalog® Mix25. At the last visit of the first treatment period, the patients completed pen device questionnaires and the WHO Diabetes Treatment Satisfaction Questionnaire (DTSQ) and then changed to the alternate insulin treatment. At the end of the 2nd 12-week treatment period, patients again completed the pen device questionnaires, the DTSQ and a comparative questionnaire asking which device they would prefer to continue to use after the trial. Treatment with NovoMix® 30 and Humalog® Mix25 were comparable with respect to HbA_{1c}, prandial blood glucose increment, postprandial blood glucose and episodes of hypoglycemia at the end of the trial. Patient treatment satisfaction, as measured by DTSQ was similar for both groups. For the device specific questionnaires, NovoMix® 30 FlexPen® was evaluated as slightly superior to Humalog® Mix25 Pen in 15 of 16 device features assessed (all $p < 0.001$). Approximately 75% of patients preferred to continue with NovoMix® 30 FlexPen® after the trial was completed.

Pediatrics:

The safety and efficacy of NovoMix® 30 were compared to biphasic human insulin 30/70 (BHI 30) in a double-blind crossover trial in 54 children, aged 6-12 years. The incidence of all hypoglycemic episodes was significantly lower for NovoMix® 30 than for BHI 30 by approximately 10%. No safety concerns were raised during the trial. However, after 12 weeks of treatment it could not be demonstrated that treatment with NovoMix® 30 was non-inferior to treatment with BHI 30 with respect to HbA_{1c} and serum fructosamine. The data available are inadequate to establish the effectiveness in children.

DETAILED PHARMACOLOGY

Insulin aspart is an analogue of human insulin, in which the amino acid, proline, in position 28, has been replaced by aspartic acid. This modification was designed to target the part of the molecule responsible for self association. Due to charge repulsion, insulin aspart has a reduced tendency to self associate. This causes insulin aspart to be absorbed more rapidly, resulting in faster action. Insulin aspart is designed to be similar to human insulin in all other aspects.

The biological activity of insulin aspart has been evaluated *in vivo* in mouse, rabbit and pig and, *in vitro* in a free fat cell assay.

In a comparison of hypoglycemic activity of insulin aspart and human insulin in the diabetic ob/ob mouse, insulin aspart reduced moderate hyperglycemia to a similar extent as an equimolar dose of human insulin.

The molar potency of insulin aspart was compared to that of a human insulin standard using the mouse blood glucose assay according to Ph.Eur. and the rabbit blood sugar method according to USP. Using the mouse blood glucose assay, the potency of three different batches of insulin aspart was determined to be 104.4% (95% confidence limits: 96.1-113.4%), 105.4% (93.8-118.3%), and 104.8% (94.3-116.5%) relative to the first international human insulin standard. Thus, the potency of insulin aspart is not significantly different from that of human insulin in the mouse blood glucose assay. The molar potency of insulin aspart is defined as 1U = 6 nmol. Potency estimates for insulin aspart determined by the rabbit blood sugar assay were equivalent to those determined by the mouse blood glucose assay.

Studies in pigs show that equimolar amounts of insulin aspart and human insulin have similar effects on blood glucose after i.v. administration, and that insulin aspart has a faster action than human insulin after s.c. administration.

In the free fat cell bioassay, the potency of insulin aspart was determined to be 102.7 % (95% confidence limits: 99.6-105.8%) relative to a human insulin standard. Thus, the potency of insulin aspart is not significantly different from that of human insulin in free fat cells.

The performed bioassays show that the potency of insulin aspart is equal to that of human insulin. A competitive ligand binding analysis using confluent HepG2 cells explored the relative binding affinities of insulin aspart and human insulin for the insulin receptor. There was no difference in their affinity. The affinity of insulin aspart for the insulin receptor was determined to be 92.2% (95% confidence limits 82.0-103.7%) of that of human insulin using HepG2 cells and to 92% of that of human insulin using solubilised receptors.

A very low affinity for the human IGF-1 receptor on HepG2 cells was also demonstrated; 68.8% compared to human insulin and about 1/1000th of the binding affinity of IGF-1 itself.

These studies show that insulin aspart has almost identical biological properties to human insulin, including affinity for the specific insulin receptor, and similar on- and off-rates at that receptor.

Cardiovascular studies in anaesthetized rats and pigs plus a range of standard behavioural and organ function test and interaction studies have been conducted. Dose levels used in rodents were up to 100 times higher than the expected human therapeutic dose of 1 U/kg. In cats and pigs the high dose was 4 times higher than the expected human therapeutic dose due to the higher sensitivity of these species.

Table 1

Test	Insulin Aspart/ Human Insulin(HI)	Results
Irwin Observation Test, mice	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No difference from human insulin was observed
Locomotor Activity, rats	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No consistent effect
Rotarod Performance, mice	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No effects
Hexobarbital induced sleeping time, mice	1,10 or 100 U/kg i.v. HI 100 IU/kg IV	No difference from human insulin was observed
Ethanol induced sleeping time, mice	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No difference from human insulin was observed
Anti-convulsant activity, mice	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No effects
Pro-convulsant activity, mice	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No effects
Analgesic effect on acetic acid induced writhing	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No effects
Effects on body temperature	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No effects
Isolated guinea-pig ileum	3.6, 36 or 360 mU/ml HI: 360 mIU/ml	No effects

Test	Insulin Aspart/ Human Insulin(HI)	Results
Autonomic nervous system in anaesthetised cat	0.4, 1.0 and 4.0 U/kg IV, HI: 0.4, 1.0 and 4.0 IU/kg IV	No difference from human insulin was observed
Cardiovascular and Respiratory Systems in anaesthetised rat	1,10 and 100 U/kg IV, HI: 1,10 and 100 IU/kg IV	No effects
Cardiovascular and Respiratory Systems in anaesthetised pig	0.4, 1.0 and 4.0 U/kg IV. HI: 0.4, 1.0 and 4.0 IU/kg IV	No difference from human insulin was observed
Gastrointestinal Motility in Mice	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No effects
Renal Function in Rats	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No effects in general

TOXICOLOGY

Acute Toxicity

Table 2 - Results of Acute Toxicity Studies with Insulin aspart

Species, Strain, Route	(M+F) Animals per group	Doses U/kg	Results
Mouse NMRI, SC	5 + 5	0, 62.5, 250, 1000, 4000	Highest non-lethal dose: 4000U/kg in males and 250U/kg in females.
Mouse, CD1, SC	5 + 5	0, 62.5, 250, 1000, 4000	Highest non-lethal dose: 4000U/kg
Mouse, NMRI, IV	5 + 5	0, 62.5, 250, 1000, 4000	Highest non-lethal dose: 4000U/kg In males and 1000 u/kg in females
Rat, S.D. SC	5 + 5	0, 62.5, 250, 1000, 4000	Highest non-lethal dose: 4000U/kg
Rat, S.D. SC	5 + 5	0, 62.5, 250, 1000, 2000	Highest non-lethal dose: 2000Ukg

Species, Strain, Route	(M+F) Animals per group	Doses U/kg	Results
Rat, S.D. SC	5 + 5	0, 62.5, 250, 1000, 4000	Highest non-lethal dose: 4000U/kg
Rat, S.D. IV	5 + 5	0, 62.5, 250, 1000, 4000	Highest non-lethal dose: 4000 U/kg
Dog, Beagle, SC.	1 + 1	4, 8, 16, 32, 64 64 Old process	Highest non-lethal dose: 64U/kg Apart from hypoglycemia no treatment-related signs or changes

The results of the acute toxicity testing in rodents are dominated by reports of non-fatal convulsions and instances of ptosis, both attributed to hypoglycemia. The pattern of effects was that expected for any insulin given in high doses.

Long-term Toxicity

Table 3 - Results of long-term toxicity studies with insulin aspart

Species	Strain	Number of groups and size	Dosing Method	Duration (Weeks)	Dose level (U/kg/day)	Results
Rat	Sprague-Dawley	5 Groups 10M, 10F/group, main 9M, 9F/group, satellites 5M, 5F in groups 1, 4 & 5 reversibility assessment	SC	4 weeks + 4 week recovery in groups 1, 4 & 5	0, 5, 25, 100 + 100	Hypoglycemia, increased food consumption and weight gain. No unexpected observations.
Rat	Sprague-Dawley	4 Groups 10M, 10F	SC	4 weeks	0, 12.5, 50, 200	Hypoglycemia. No unexpected observations.
Rat	Mol: WIST	4 Groups 15M, 15F	SC	13 weeks	0, 12.5, 50, 200	Hypoglycemia, increased weight gain. No unexpected observations.
Rat	Sprague-Dawley	4 Groups 32M, 32F Satellites included	SC	52 weeks	Top dose levels 100 bid for 24 weeks, 50 bid weeks 25-26, 100 od weeks 27-37, 75 od from week 38-52. Lower dose levels 5 and 25U/kg/bid for 26 weeks 10 and 50 od for 27-52 weeks. Controls.	Hypoglycemia, increased food and water consumption and weight gain. Excess of mammary tumors in high dose females.
Rat	Sprague-Dawley	4 Groups 20F	SC	52 weeks	200 per drug substance. Insulin aspart, human insulin, control.	Mammary tumor-incidence higher in insulin aspart group equal to human insulin both being higher than controls.
Dog	Beagle	4 groups	SC	4weeks	0, 0.25, 0.5, 1.0	Hypoglycemia.

Species	Strain	Number of groups and size	Dosing Method	Duration (Weeks)	Dose level (U/kg/day)	Results
		3M, 3F/group, main 1M, 1F in groups 1 & 4 reversibility assessment		(+ 4 week recovery in groups 1 & 4)	Bid	No unexpected observations.
Dog	Beagle	3 Groups 4M, 4F	SC	13 weeks	0,1, 4	Hypoglycemia. No unexpected observations.
Dog	Beagle	4 Groups 4M, 4F	SC	52 weeks	0, 0.25, 0.5, 1.0 bid for 28 weeks same daily dose od from week 29-52. HI- 1.0 bid 28 weeks 2.0 od from 29-52	Hypoglycemia. No unexpected observations.

Carcinogenicity

Carcinogenicity trials have not been performed with NovoMix[®] 30. A series of repeated dose trials in animals (including 52 weeks dosing in rats and dogs) showed that none of the effects observed with insulin aspart differed from those observed with regular human insulin. In vitro trials showed that the mitogenicity of insulin aspart does not differ from that observed with regular human insulin. Animal trials on the mutagenic potential of insulin aspart and regular human insulin did not show any difference between the two products.

Mutagenicity

A comprehensive range of experiments have been completed and, insulin aspart gave negative results. Human insulin also gave negative results. It is concluded that insulin aspart is not a genotoxicant.

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Important: Please Read

PART III: CONSUMER INFORMATION

If you have difficulties with reading this document, ask a family member or a friend for help with reading it.

This document is available in large print format by contacting Novo Nordisk Canada Inc., at 1-800-465-4334

**NovoMix[®] 30 Penfill[®] and
NovoMix[®] 30 FlexPen[®]**
30% soluble insulin aspart and
70% insulin aspart protamine crystals

Suspension for injection 3 mL

This leaflet is Part III of a three-part 'Product Monograph' published when NovoMix[®] 30 was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about NovoMix[®] 30. Contact your doctor or pharmacist if you have any questions about the drug.

Read all of this leaflet carefully before you start using your insulin. Keep this leaflet. You may need to read it again. If you have further questions, please ask your doctor, Diabetes Nurse Educator or pharmacist.

This medicine is prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

ABOUT THIS MEDICATION

A direction leaflet containing information for the patient is included in each package.

What is NovoMix[®] 30

NovoMix[®] 30 (30% soluble insulin aspart and 70% insulin aspart protamine crystals) is an insulin analogue used to treat diabetes. NovoMix[®] 30 is a mixture of rapid-acting insulin analogue (30%) and long-acting insulin analogue

(70%). This means that it will start to lower your blood sugar 10 to 20 minutes after you take it, has a maximum effect of between 1 and 4 hours and the effect lasts for up to 24 hours.

NovoMix[®] 30 is indicated for:

- the treatment of adult patients with diabetes mellitus who require insulin for the control of hyperglycemia.

When NovoMix[®] 30 should not be used

Do not use NovoMix[®] 30:

- ▶ **If you feel a hypo** coming on (a hypo is short for a hypoglycemic reaction or low blood sugar). See '*What to do in an emergency*', for more about hypos.
- ▶ **If you are allergic (hypersensitive)** to soluble insulin aspart with insulin aspart protamine crystals, metacresol or any of the other ingredients in this insulin. Look out for the signs of an allergic reaction (see '*Possible side effects*').

What the medicinal ingredient is

The active ingredient in NovoMix[®] 30 is a mixture of insulin aspart made by recombinant DNA technology in *Saccharomyces cerevisiae* (30% insulin aspart in a soluble fraction and 70% insulin aspart crystallized with protamine).

What the important nonmedicinal ingredients are:

glycerol, phenol, metacresol, zinc (as chloride), sodium chloride, disodium phosphate dihydrate, protamine sulphate, sodium hydroxide, hydrochloric acid, water for injections

What dosage forms NovoMix[®] 30 comes in

NovoMix[®] 30 is available from Novo Nordisk Canada in the following format:

- NovoMix[®] 30 Penfill[®] 3 mL cartridge (designed for use with Novo Nordisk Insulin Delivery Devices)
- NovoMix[®] 30 FlexPen[®] 3 mL prefilled pen

NovoMix[®] 30 Penfill[®] cartridges are designed for use with Novo Nordisk Insulin Delivery Devices. NovoMix[®] 30 Penfill[®] and NovoMix[®] 30 FlexPen[®] are designed for use with NovoFine[®]. Novo Nordisk cannot be held responsible for malfunctions occurring as a consequence of using NovoMix[®] 30 Penfill[®] cartridges in combination with products that do not meet the same specifications or quality standards.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- NovoMix[®] 30 should be given immediately before a meal because of the fast onset of action (start of the meal should be not more than 5-10 minutes after injection) (see "*Proper Use of This Medication*").

Before you use NovoMix[®] 30

Before you use NovoMix[®] 30 talk to your doctor or pharmacist:

- ▶ **If you have trouble** with your kidneys or liver, or with your adrenal, pituitary or thyroid glands.
- ▶ **If you drink alcohol:** watch for signs of a hypo.
- ▶ **If you exercise more than usual** or if you want to change your usual diet.
- ▶ **If you are ill:** continue taking your insulin.
- ▶ **If you have an infection, fever or an operation** you may need more insulin than usual.
- ▶ **If you go abroad:** travelling over time zones may affect your insulin needs and timing of your injections. Consult your doctor if you are planning such travel..
- ▶ **If you are pregnant, or planning a pregnancy or are breastfeeding** please contact your doctor for advice.
- ▶ **If you drive or use tools or machines:** watch for signs of a hypo. Your ability to concentrate or to react will be less during a hypo. Please keep this in mind in all situations where you might put yourself and

others at risk (e.g., driving a car or operating machinery). Never drive or use machinery if you feel a hypo coming on.

Discuss with your doctor whether you should drive or use machines at all, if you have a lot of hypos or if you find it hard to recognize hypos.

Before you travel, check with your physician or pharmacist on the availability of NovoMix[®] 30 in other countries. If possible, bring enough NovoMix[®] 30 with you on your trip.

INTERACTIONS WITH THIS MEDICATION

NovoMix[®] 30 should not be mixed with any other insulin product.

When you use other medicines

Many medicines affect the way glucose works in your body and this may influence your insulin dose. Listed below are the most common medicines, which may affect your insulin treatment. Talk to your doctor or pharmacist if you take, or change any other medicines, even those not prescribed.

Your need for insulin may change if you also take: oral antidiabetic products, monoamine oxidase inhibitors (MAOI); beta-blockers; angiotensin converting enzyme (ACE) inhibitors, salicylates (aspirin); anabolic steroids; glucocorticoids (except topical administration); oral contraceptives; thiazides; thyroid hormones; sympathomimetics; danazol; octreotide and sulphonamides.

PROPER USE OF THIS MEDICATION

How to use NovoMix[®] 30

Talk about your insulin needs with your doctor and Diabetes Nurse Educator. Follow their advice carefully. This leaflet is a general guide only.

When NovoMix[®] 30 is used in combination with metformin the dosage should be adjusted.

If your doctor has switched you from one type or brand of insulin to another, your dose may have to be adjusted by your doctor.

NovoMix[®] 30 should be given immediately before a meal. When necessary, NovoMix[®] 30 may

also be given soon after the meal. It is recommended that you measure your blood glucose regularly.

A NovoMix[®] 30 FlexPen[®] or Penfill[®] cartridge must not be used by more than one person.

Before using NovoMix[®] 30 Penfill[®]:

- ▶ **Check the label** to make sure you have the right type of insulin.
- ▶ **Always use a new needle** for each injection to prevent contamination.
- ▶ **Always check the Penfill[®] cartridge**, including the rubber stopper (plunger). Don't use it if any damage is seen or if there is a gap between the rubber stopper and the white barcode label. Take it back to your supplier or call Novo Nordisk Canada at 1 800 465-4334 for assistance. See your Novo Nordisk Insulin Delivery Device manual for further instructions.
- ▶ Before use, check that the Penfill[®] cartridge is intact (no cracks). Do not use the Penfill[®] cartridge if any damage is seen or if more of the rubber piston is visible than equal to the width of the white bar code band.
- ▶ The first time you use the NovoMix[®] 30 Penfill[®] allow it to reach room temperature and then roll it horizontally between your palms 10 times and then turn upside down 10 times. (See Package Insert for detailed diagrams and instructions.)
- ▶ Repeat the rolling and moving procedure until the liquid appears uniformly white and cloudy.
- ▶ For all subsequent injections move the insulin delivery device, with the cartridge inside it up and down at least 10 times until the liquid appears uniformly white and cloudy. (See Package Insert for detailed diagrams and instructions.)

How to use NovoMix[®] 30 FlexPen[®]

- Allow the **NovoMix[®] 30 FlexPen[®]** to reach room temperature and then roll it horizontally between your palms 10 times and then turn upside down 10 times. (See Package Insert for detailed diagrams and instructions.)
- Remove air from the prefilled insulin pen before each injection until a drop of insulin appears at the tip of the needle.
- Do not use **NovoMix[®] 30 FlexPen[®]** if you need to make **more** than 6 air shots before the first injection.
- Take care not to drop or knock your prefilled insulin pen.

- Do not use the residual scale to measure your dose of insulin.
- Do not refill **NovoMix[®] 30 FlexPen[®]**.

Do not use NovoMix[®] 30:

- ▶ **In insulin infusion pumps.**
- ▶ **If the Penfill[®] cartridge, Novo Nordisk Insulin Delivery Device or FlexPen[®] containing the insulin is dropped, damaged or crushed;** there is a risk of leakage of insulin.
- ▶ **If the insulin has not been stored correctly** or if it has been frozen (see 'How to Store NovoMix[®] 30').
- ▶ **If the insulin is not uniformly white and cloudy** when it is mixed.
- ▶ **If clumps of material are present** or if solid white particles stick to the bottom or the wall of the cartridge giving a frosted appearance.

Do not refill a NovoMix[®] 30 Penfill[®] cartridge.

NovoMix[®] 30 Penfill[®] cartridges are designed to be used with Novo Nordisk Insulin Delivery Devices and NovoFine[®] needles as part of The All In-One System[®].

If you are treated with NovoMix[®] 30 Penfill[®] and another insulin in Penfill[®] cartridge, you should use two Novo Nordisk Insulin Delivery Devices, one for each type of insulin.

How to use this insulin

NovoMix[®] 30 is for injection under the skin (subcutaneously). Never inject your insulin directly into a vein or muscle.

Always vary the site you inject within the same region, to avoid lumps (see 'Possible side effects'). The best places to give yourself an injection are: the front of your thighs; the front of your waist (abdomen); or the upper arm. Your insulin will work more quickly if you inject around the waist.

You should always measure your blood glucose regularly.

How to inject this insulin

- ▶ **Inject the insulin under the skin.** Use the injection technique advised by your doctor or Diabetes Nurse Educator and described in your Novo Nordisk Insulin Delivery Device manual.

- ▶ **Keep the needle under your skin** for at least 6 seconds to make sure that the full dose has been delivered.
- ▶ **After each injection** be sure to remove the needle. Otherwise, insulin may leak out when the temperature changes.

Overdose

Causes of a hypo:

You get a hypo if your blood sugar gets too low. This might happen:

- If you take too much insulin.
- If you eat too little or miss a meal.
- If you exercise more than usual.

If your blood sugar gets too high:

Your blood sugar may get too high (this is called hyperglycemia).

The warning signs appear gradually.

They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed dry skin; a dry mouth and a fruity (acetone) smelling breath.

If you get any of these signs: test your blood sugar level; test your urine for ketones if you can; then seek medical advice right away.

These may be signs of a very serious condition called diabetic ketoacidosis. If you don't treat it, this could lead to diabetic coma and death.

Causes of hyperglycemia:

- Forgetting to take your insulin.
- Repeatedly taking less insulin than you need.
- An infection or fever.
- Eating more than usual.
- Exercising less than usual.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

What to do in an emergency

If you get a hypo:

A hypo means your blood sugar level is too low.

The warning signs of a hypo may come on suddenly and can include: cold sweat; cool pale

skin; headache; rapid heart beat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; and difficulty concentrating.

If you get any of these signs: eat glucose tablets or a high sugar snack (sweets, biscuits, fruit juice), then rest.

Don't take any insulin if you feel a hypo coming on.

Carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.

Tell your relatives, friends and close colleagues that if you pass out (become unconscious); they must turn you on your side and get medical help right away. They must not give you anything to eat or drink as it could choke you.

- ▶ **If severe hypoglycemia is not treated**, it can cause brain damage (temporary or permanent) and even death.
- ▶ **If you have a hypo that makes you pass out**, or if you get a lot of hypos, talk to your doctor. The amount or timing of your insulin dose, the amount of food you eat or the amount of exercise you do, may need to be adjusted.

Using glucagon

You may recover more quickly from unconsciousness with an injection of the hormone glucagon given by someone who knows how to use it. If you are given glucagon you will need to eat glucose or a sugary snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital. Contact your doctor or hospital emergency after an injection of glucagon: you need to find the reason for your hypo in order to avoid getting more.

Possible side effects

Like all medicines, NovoMix® 30 can have side effects although not everybody gets them. The most common side effect is low blood sugar (hypoglycemia). See the advice in '*What to do in an emergency*'.

Less commonly reported side effects (less than 1 in 100)

Vision problems When you first start your insulin treatment, it may disturb your vision, but the reaction usually disappears.

Changes at the injection site (Lipodystrophy)

If you inject yourself too often in the same site, fatty tissue under the skin at this injection site may shrink (lipoatrophy) or thicken (lipohypertrophy). Changing the site with each injection may help to prevent such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or Diabetes Nurse Educator because these reactions can become more severe, or they may change the absorption of your insulin at this site.

Signs of allergy Reactions (redness, swelling, itching) at the injection site may occur (local allergic reactions). These usually disappear after a few weeks of taking your insulin. If they do not disappear, see your doctor.

Seek medical advice immediately:

- If signs of allergy spread to other parts of your body, or
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty-breathing; have a rapid heart beat; feel dizzy.

• **You may have a very rare serious allergic reaction** to NovoMix[®] 30 or one of its ingredients (called a systemic allergic reaction). Also read the information in 2 'Before you use NovoMix[®] 30'.

Diabetic retinopathy If you have diabetic retinopathy and your blood glucose levels improve very fast, the retinopathy may get worse. Ask your doctor about this.

Swollen joints When you start taking insulin, water retention may cause swelling around your ankles and other joints. This soon disappears.

Rarely reported side effects
(less than 1 in a 1,000)

Painful neuropathy If your blood glucose levels improve very fast, you may get nerve related pain – this is called acute painful neuropathy and is usually transient.

If any of the side effects get serious, or if you notice any side effects, including those not

mentioned in this leaflet, please inform your doctor, Diabetes Nurse Educator or pharmacist.

HOW TO STORE IT

How to store NovoMix[®] 30

Keep out of the reach and sight of children.

NovoMix[®] 30 that is not being used is to be stored in the fridge between 2°C - 10°C, not in or near the freezer section or cooling element. Do not freeze.

NovoMix[®] 30 that is being used or is about to be is not to be kept in the refrigerator. You can carry it with you and keep it at room temperature (not above 30°C) for up to 4 weeks.

Always keep your Penfill[®] cartridge and FlexPen[®] in the outer carton when you are not using it, in order to protect it from light.

NovoMix[®] 30 should be protected from excessive heat and sunlight.

Do not use NovoMix[®] 30 after the expiry date printed on the label and carton. The expiry date refers to the last day of that month.

NovoMix[®] 30 should not be disposed of in waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse drug reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of the side effect, please contact your health care professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

How to store NovoMix® 30 looks like and package content:

NovoMix® 30 comes as a white suspension in packages of 5 x 3 ml Penfill® cartridge per carton.

1 ml contains 100 U (units) of insulin aspart
1 prefilled pen contains 3 ml equivalent to 300 U

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Novo Nordisk A/S

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Reference: 1 Canadian Diabetes Association
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Prevention and Management of Diabetes in
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