PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Schedule D

NovoMix® 30

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

Suspension for Injection, 100 Units/mL

Subcutaneous injection

Professed

Antidiabetic Agent

ATC code: A10AD05

long-acting combined with fast-acting

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Date of Initial Authorization:
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RECENT MAJOR LABEL CHANGES

4.4 Administration	03/2021
7 Warnings and Precautions	03/2021

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

NovoMix® 30 (30% soluble insulin aspart and 70% insulin aspart protamine crystals) is indicated for:

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

1.1 Pediatrics

Pediatrics (<16 years of age): No adequate data are available to establish the effectiveness in pediatrics.

1.2 Geriatrics

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.

2 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, STRENGTHS, COMPOSITION AND PACKAGING*.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Hypoglycemia is the most common adverse effect of insulin products. As with all insulin products the timing of hypoglycemia may differ according to type of insulin product. Glucose monitoring shall be performed for all patients with Diabetes Mellitus treated with insulins. (see *HYPOGLYCEMIA AND OVERDOSAGE*)
- Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma or even death. (see *HYPOGLYCEMIA AND OVERDOSAGE*)
- Any transfer of insulin products should be made cautiously and only under medical supervision. (see *WARNINGS AND PRECAUTIONS – Transferring Patient from Other Insulins*)
- NovoMix 30 is a dual release suspension. Due to the rapid onset of action, the injection of NovoMix® 30 should immediately be followed by a meal (within 5-10 minutes) or should be given immediately after the meal. (see *DOSAGE AND ADMINISTRATION – Recommended dose and dosage adjustment*).
- Long-acting insulin products and/or suspensions MUST NOT be administered Intravenously (IV) or be used in insulin infusion pumps.(see *DOSAGE AND ADMINISTRATION*)
- Insulin products shall not be mixed with any other insulin unless clearly indicated and done

under medical supervision. (see *WARNINGS AND PRECAUTIONS*)

- NovoMix® 30 shall not be used if the resuspended liquid does not appear uniformly white and cloudy or if it has formed a deposit of solid particles on the wall of the cartridge which is present after resuspending. (see *DOSAGE AND ADMINISTRATION*)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Patients being initiated on insulin can be started on NovoMix® in the same manner as they would be on animal-source or human insulin.
- Changes for patients being transferred from other insulin to NovoMix® should be made as directed by a physician.
- In clinical trials, patients were transferred on a unit to unit basis from human premixed 30/70 or human NPH to NovoMix®. The doses of meal-related and basal insulin were then changed according to the patients' needs and local practice.

4.2 Recommended Dose and Dosage Adjustment

Due to its faster onset of action, NovoMix® 30 should be given immediately before the meal. The injection should not be more than 5-10 minutes before the start of a meal. When necessary, NovoMix® 30 may be given immediately after the meal.

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.

The dosing of NovoMix® 30 should regularly be adjusted according to blood glucose measurements. Adjustment dosage may also be necessary if patients undertake increased physical activity or change their usual diet. Exercise taken immediately after a meal may increase the risk of hypoglycemia.

4.4 Administration

NovoMix® 30 is administered subcutaneously by injection in the abdominal wall, the thigh, the upper arm, the deltoid region or the gluteal region. Care should be taken to avoid entry into a blood vessel. Injection sites should be rotated within the same region from one injection to the next so that the same site is not used more than approximately once a month in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS). 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 or be used in infusion pumps.

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.

Before travelling between different time zones the patient should seek the doctors' advice since this means that the patient has to take the insulin and meals at different times.

5 OVERDOSAGE

Hypoglycemia may occur as a result of an excessive dose of insulin relative to food intake, energy expenditure, or both. 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, anxiousness, 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 (0.5-1 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 10-15 minutes. Upon regaining consciousness, administration of an oral carbohydrate is recommended for the patient in order to prevent relapse.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognize the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous injection.	Suspension for injection, 100 Units/mL 3 mL Penfill® cartridges 1 mL of the solution contains 100 Units of soluble insulin aspart and protamine-crystallized	Disodium hydrogen phosphate dihydrate, glycerol, metacresol, phenol, protamine sulphate, sodium chloride, water for injections and zinc (as chloride). *Sodium hydroxide and/or hydrochloric acid may be added to adjust the pH.

	insulin aspart in the 30/70 ratio (equivalent to 3.5 mg). Package Size:: 5 x 3 mL.	

NovoMix® 30 is available in 3 mL Penfill® cartridges.

Needles and NovoMix® 30 Penfill® in a Novo Nordisk Insulin Delivery Devices should never be shared between patients, even if the needle is changed. The cartridge must not be refilled.

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.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

Inadequate dosing or discontinuation of treatment, especially in type 1 diabetes, may lead to hyperglycemia and diabetic ketoacidosis. Usually the first symptoms of hyperglycemia develop gradually over a period of hours or days. They include thirst; increased frequency of urination; nausea; vomiting; drowsiness; flushed dry skin; dry mouth; loss of appetite as well as acetone odour of breath. In type 1 diabetes, untreated hyperglycemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

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

General

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.

Insulin aspart differs from regular human insulin by its rapid onset and shorter duration of action. As a result of the fast onset of action, the injection of NovoMix® 30 should immediately be followed by a meal.

Thiazolidinediones (TZDs), alone or in combination with other antidiabetic agents (including insulin), can cause heart failure and oedema. The combination of insulin with a TZD is not indicated for the treatment of type 2 Diabetes Mellitus. Please refer to the respective TZD product monograph *WARNINGS AND PRECAUTIONS* information when the use of these

drugs in combination with any insulin, including NovoMix® 30, is contemplated.

Never Share a NovoMix® 30 Penfill® in a Novo Nordisk Insulin Delivery Device Between Patients. NovoMix® 30 Penfill® in a Novo Nordisk Insulin Delivery Device should never be shared between patients, even if the needle if changed. Sharing poses a risk for transmission of blood-borne pathogens

Carcinogenesis and Mutagenesis
See PART II: Scientific Information – Toxicology.

Driving and Operating Machinery
No studies on the effects on the ability to drive and use machines have been performed. Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

Endocrine and Metabolism
Hypoglycemia
As with other insulins, hypoglycemia is the most frequently occurring undesirable effect of insulin therapy. Such reactions following treatment with NovoMix® 30 are mostly mild and easily managed.

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of NovoMix® 30. 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.

Patients, whose blood glucose control is greatly improved, e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycemia, and should be advised accordingly. Usual warning symptoms may disappear in patients with longstanding diabetes. Hypoglycemia may occur if the insulin dose is too high in relation to the insulin requirement. (see *ADVERSE REACTIONS and HYPOGLYCEMIA AND OVERDOSAGE*). Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia.

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

Hypoglycemia can occur regardless of what type of insulin you take and can cause fatigue, sweating, heart palpitations, disturbed behaviour, hunger, convulsions, loss of consciousness, temporary or permanent impairment of brain function, or, in extreme circumstances, even death which can occur without recognizable symptoms.

Some people may not recognize when their blood sugar drops low. 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).

Patients should be advised to take precautions to avoid hypoglycemia while driving. This is particularly important in those who have reduced or absent awareness of the warning signs of

hypoglycemia or have frequent episodes of hypoglycemia. The advisability of driving should be considered in these circumstances.

Glucose monitoring is recommended for all patients with diabetes.

Hyperglycemia
Inadequate dosing or discontinuation of insulin treatment, especially in type 1 diabetes, may lead to hyperglycemia and diabetic ketoacidosis. Usually the first symptoms of hyperglycemia develop gradually over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite as well as acetone odour of breath. In type 1 diabetes, untreated hyperglycemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

Hypokalemia
All insulin products, including NovoMix®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, patients taking medications sensitive to serum potassium concentrations, or patients losing potassium through other means (e.g., diarrhea). (see Adverse Reactions)

Hepatic/Biliary/Pancreatic
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*)

Immune

Local Allergic Reaction
As with any insulin therapy, injection site reactions may occur and include pain, redness, itching, hives, swelling, bruising and inflammation. Continuous rotation of the injection site within a given area reduces the risk of developing these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of NovoMix® 30. Localized reactions and generalized myalgias have been reported with injected metacresol, which is excipient in NovoMix®30. (see Skin and subcutaneous tissue disorders)

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.

Antibody Production
Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycemia.

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.

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.

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.

Transferring Patients from Other Insulins
When patients are transferred between different types of insulin products, including animal insulins, the early warning symptoms of hypoglycemia may have changed or become less pronounced than those experienced with their previous insulin. Transferring a patient to a new type or brand of insulin should be done only under strict medical supervision. Changes in insulin strength, timing of administration, manufacturer, type (e.g. regular, NPH or insulin analogs), or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dosage. Concomitant oral anti-diabetic treatment may also need to be adjusted. If an adjustment is needed, it may be done with the first doses or during the first weeks or months and under medical supervision.

Mixing of Insulin
Mixing of NovoMix® 30 is generally not recommended. Mixing one insulin formulation with another insulin formulation may change the pharmacokinetic and/or pharmacodynamic profile of action of the combined mixture in an unpredictable manner.

Avoidance of accidental mix-ups/medication errors
Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between NovoMix® and other insulin products

Sexual Health
Reproduction/Function
There is no information on teratogenicity of NovoMix® 30 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.

Skin and subcutaneous tissue disorders

Subcutaneous administration of insulin products, including Novomix® can result in lipoatrophy (thinning of adipose tissue) or lipohypertrophy (thickening of adipose tissue) or localized cutaneous amyloidosis (skin lumps) which may affect insulin absorption.

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. Patients should be advised to consult their health professional if they notice any of these conditions and before changing the injection site. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site from an affected to an unaffected area, and dose adjustment of antidiabetic medications may be considered.

7.1 Special Populations

7.1.1 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.

7.1.2 Breast-feeding

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.

7.1.3 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)

7.1.4 Geriatrics

The effect of age on the pharmacokinetics and pharmacodynamics of NovoMix® 30 has not been studied. As with all insulins, in elderly patients glucose monitoring should be intensified and dosage adjusted on an individual basis.

Other

The presence of diseases such as Acromegaly, Cushing's syndrome, Hyperthyroidism and Pheochromocytoma can complicate the control of diabetes mellitus.

8 ADVERSE REACTIONS

8.1 Adverse 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.

Lipodystrophy (including lipohypertrophy, lipoatrophy) and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. (see WARNINGS AND PRECAUTIONS).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

NovoMix® 30 has been evaluated for safety in patients with type 1 and type 2 diabetes in an 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).

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				
Headache	29	29%	17	17%
Sensory disturbance	10	10%	12	12%
Hyporeflexia	9	9%	9	9%
Neuropathy	8	8%	8	8%
Migraine	3	3%	4	4%
Cramps legs	3	3%	2	2%
Dizziness	2	2%	3	3%
Vertigo	2	2%	1	<1%
Neuralgia	1	<1%	3	3%
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%

	NovoMix® 30		BHI 30	
	N	(%)	N	(%)
Pain	2	2%	1	<1%
Malaise	2	2%		
Nasal polyp	2	2%		
Chest pain	1	<1%	5	5%
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%
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%		
Hyperglycemia	1	<1%	3	3%
Hypoglycemia	1	<1%	2	2%
Oedema leg				2%

	NovoMix® 30		BHI 30	
	N	(%)	N	(%)
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%		
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

8.3 Less Common Clinical Trial Adverse Reactions

(<1%) Reported in patients with type 1 or type 2 Diabetes

Eye disorders:
Uncommon (>1/1000, <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 (>1/1000, <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 reactions
Anaphylactic reactions: 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/Injections site reactions
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.

8.5 Post-Market Adverse Reactions

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 ≤ 1/1000).
- 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 ≤ 1/10,000).

- Hyperglycemia 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 ≤ 1/1000).
- 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 ≤ 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 ≤ 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 ≤ 1/10,000).

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

The following substances may reduce the insulin requirements: Oral antidiabetic drugs, monoamine oxidase inhibitors (MAOI), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids, sulphonamides and alcohol.

The following substances may increase insulin requirements: Oral contraceptives, thiazides, glucocorticosteroids, thyroid hormones, sympathomimetics, growth hormone and danazol.

Beta-blocking agents may mask the symptoms of hypoglycemia and delay recovery from hypoglycemia.

Octreotide/lanreotide may either increase or decrease insulin requirements.

Alcohol may intensify or reduce the hypoglycemic effect of insulin.

To avoid the risk of developing new or worsening heart failure, the use of TZDs in combination therapy with NovoMix® 30 is not indicated. (see *WARNINGS AND PRECAUTIONS*)

9.5 Drug-Food Interactions

Please refer to ACTION AND CLINICAL PHARMACOLOGY, Mechanism of Action and DOSAGE AND ADMINISTRATION for interactions with food and timing of food consumption,

respectively.

Drug-Lifestyle Interactions

The effect of smoking on the pharmacokinetics and pharmacodynamics of NovoMix® 30 has not been studied. The effect of obesity on the pharmacokinetics and pharmacodynamics of NovoMix® 30 has 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.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 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).

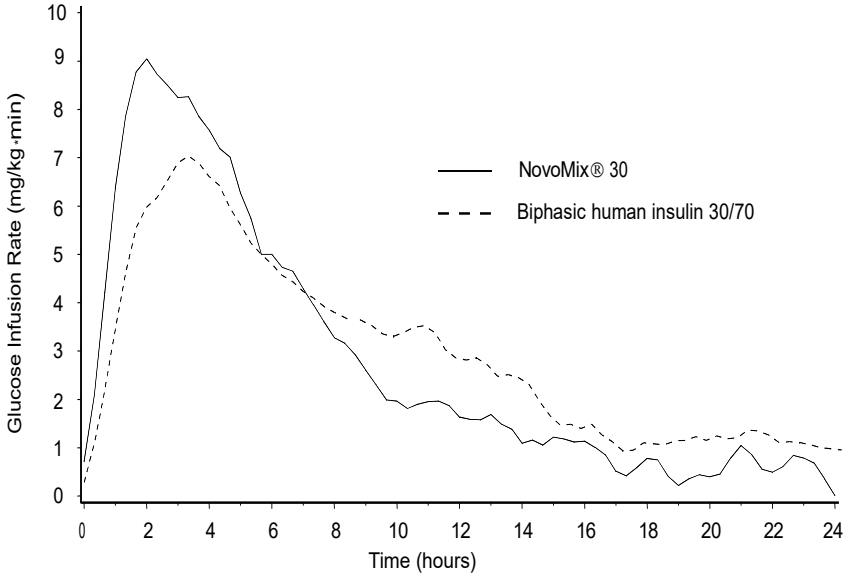


Figure 1: Pharmacodynamic activity profile of NovoMix® 30 and biphasic human insulin 30/70 in healthy subjects (ANA-033)

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.

**The pharmacodynamic response to insulin can be evaluated using a euglycemic clamp technique. The subjects are clamped to a pre-determine glucose level. Following trial insulin administration, continuous and variable glucose infusion is administered to maintain a constant, pre-determined glucose level. The glucose infusion rate (GIR) is a rather direct measure of the glucose-lowering effect of the trial insulin.*

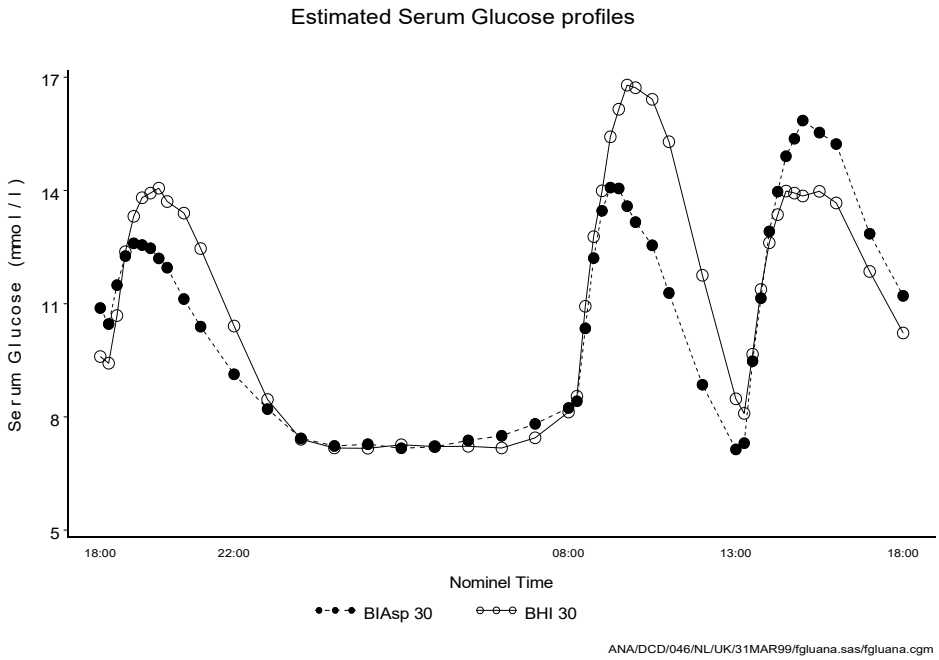


Figure 2: Estimated serum glucose levels following twice daily injection (immediately before breakfast and dinner) of NovoMix® 30 (BIAsp 30) or biphasic human insulin (BHI 30) in 13 patients with Type 2 diabetes (ANA-046).

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 10-20 minutes of injection. The maximum effect is exerted between 1 and 4 hours after injection. The duration of action is up to 24 hours.

10.3 Pharmacokinetics

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.

Table 1 - Summary of NovoMix® 30 Pharmacokinetic Parameters in Healthy Participants

	C_{max}	T_{max}	$t_{½}$ (h)
Single dose mean	On average, 50% higher than with biphasic human insulin 30/70 (Figure 3)	On average, half that for biphasic human insulin 30/70. 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	Reflecting the absorption rate of the protamine bound fraction t½, 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

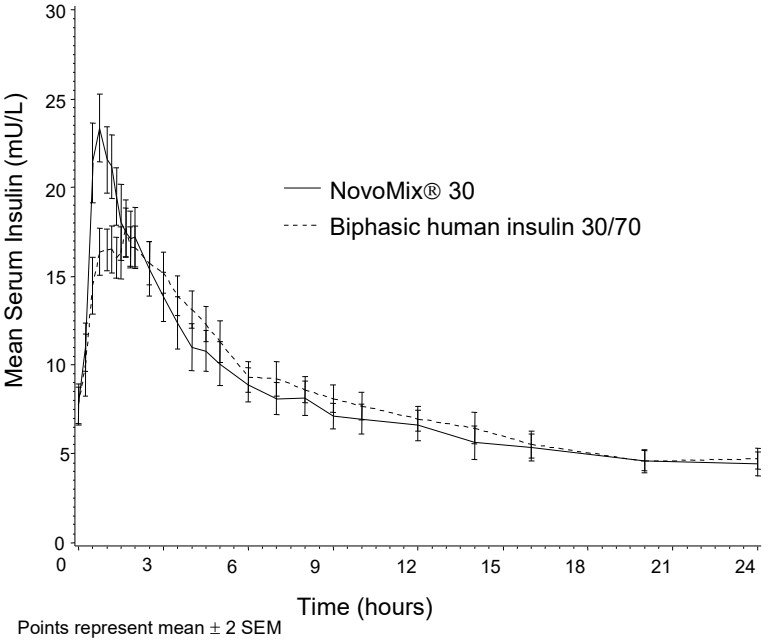


Figure 3: Mean serum insulin concentration following a single subcutaneous dose (0.2U/kg body weight) of NovoMix® 30 (solid line) and biphasic human insulin 30/70 (hatched line) in healthy subjects.

Distribution:

Insulin aspart has a low binding to plasma proteins, 0-9%.

Elimination

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.

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

Genetic Polymorphism: No specific information is available.

Ethnic origin: 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.

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 cats 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 2

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 IV, 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

Test	Insulin Aspart/ Human Insulin (HI)	Results
Isolated guinea-pig ileum	3.6, 36 or 360 mU/ml HI: 360 mIU/ml	No effects
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

11 STORAGE, STABILITY AND DISPOSAL

NovoMix® 30 should be stored between 2°C-10°C not near a freezing compartment. Do not freeze. Do not expose to excessive heat. In order to protect from light NovoMix® 30 should be kept in the outer carton.

NovoMix® 30 Penfill® cartridges in use or carried as a spare may be kept at temperatures not above 30°C for up to 4 weeks. Do not refrigerate NovoMix® 30 that is in use.

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

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

12 SPECIAL HANDLING INSTRUCTIONS

The cartridges are designed to be used with Novo Nordisk delivery devices and NovoFine® and NovoTwist® needles. Detailed instruction accompanying the cartridge and delivery system must be followed.

NovoMix® 30 Penfill® 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.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

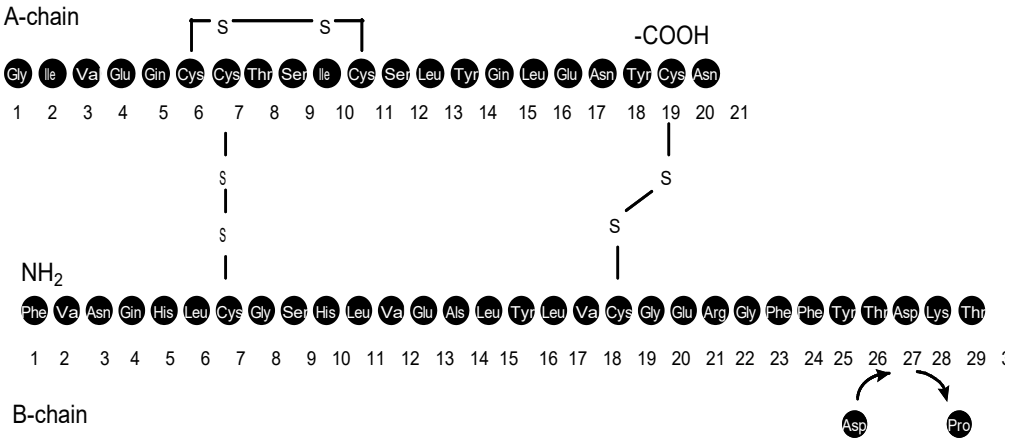
Proper name: Insulin Aspart

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

Structural formula:



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.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Estimated Mean 24-hour Serum Glucose Profiles
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.

14.2 Study Results

Estimated Mean 24-hour Serum Glucose Profiles
The shape of the 24-hour total serum glucose concentration-time profiles were statistically significantly different between treatments over time (see Figure 4 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.

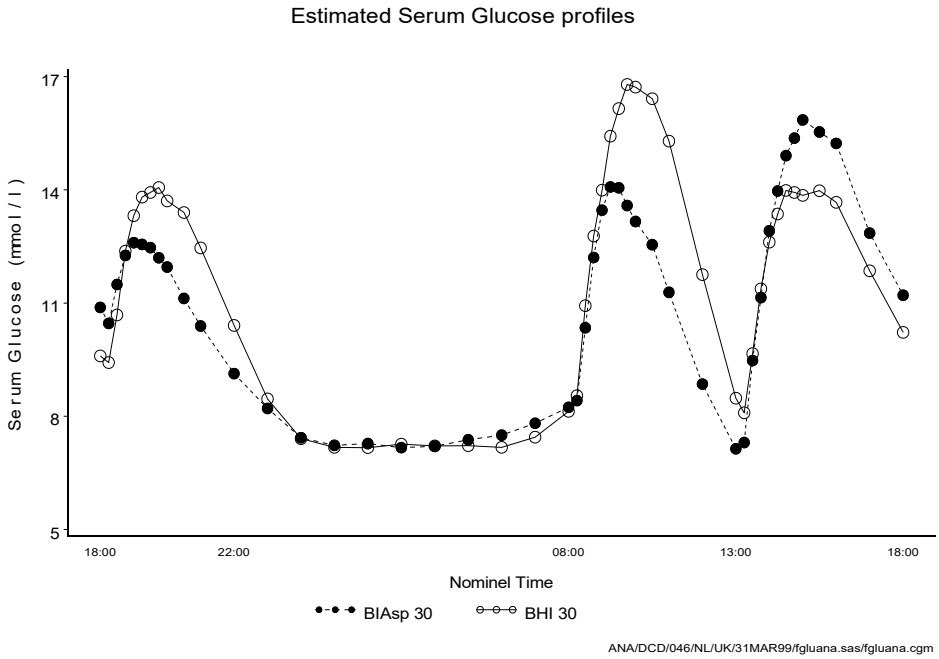


Figure 4: Estimated serum glucose levels following twice daily injection (immediately before breakfast and dinner) of NovoMix® 30 (BIAsp 30) or biphasic human insulin (BHI 30) in 13 patients with type 2 diabetes.

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 four - 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®**ge** 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 -nine subjects in the NovoMix® 30 group, -nine 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) was 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- 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 an 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 second 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.

15 NON-CLINICAL TOXICOLOGY

Acute Toxicity

Table 3 - 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
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 4- 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.

Species	Strain	Number of groups and size	Dosing Method	Duration (Weeks)	Dose level (U/kg/day)	Results
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 3M, 3F/group, main 1M, 1F in groups 1 & 4 reversibility assessment	SC	4weeks (+ 4 week recovery in groups 1 & 4)	0, 0.25, 0.5, 1.0 Bid	Hypoglycemia. 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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

NovoMix® 30

30% soluble insulin aspart and

70% insulin aspart protamine crystals

Suspension for Injection

Penfill®

Read this carefully before you start taking **NovoMix® 30** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **NovoMix® 30**.

Serious Warnings and Precautions

- Hypoglycemia is the most common adverse effect of insulin, including NovoMix® 30.
- If hypoglycemia or hyperglycemic reactions are not treated they can result in the loss of consciousness, coma or death.
- Glucose monitoring is recommended for all patients with diabetes.
- Any change of insulin should be made cautiously and only under medical supervision. This may result in dosage adjustment.
- 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) or should be given immediately after the meal. (see *'How to take NovoMix® 30'*)
- Never inject your insulin directly into a vein.
- Do not use NovoMix® 30 in insulin pumps.
- NovoMix® 30 should not be used if it is not uniformly white and cloudy after re-suspension.

What is NovoMix® 30 used for?

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

How does NovoMix® 30 work?

NovoMix® 30 (30% soluble insulin aspart and 70% insulin aspart protamine crystals) is an insulin analogue used to treat diabetes.

NovoMix® 30 is long-acting insulin analogue (70%) combined with fast-acting insulin analogue (30%). This means that it will start to lower your blood sugar 10-20 minutes after you take it, has a maximum effect of between 1 and 4 hours and the effect lasts for up to 24 hours.

What are the ingredients in NovoMix® 30?

Medicinal ingredients: The active ingredient in NovoMix® 30 is a mixture of insulin (30% insulin aspart in a soluble fraction and 70% insulin aspart crystallized with protamine).

Non-medicinal ingredients: Glycerol, phenol, metacresol, zinc (as chloride), sodium chloride, disodium phosphate dihydrate, protamine sulphate, sodium hydroxide, hydrochloric acid, water

for injections

NovoMix® 30 comes in the following dosage forms:
NovoMix® 30 is available from Novo Nordisk Canada in the following formats:

- NovoMix® 30 Penfill® 3 mL cartridge (designed for use with Novo Nordisk Insulin Delivery Devices)

NovoMix® 30 Penfill® is designed for use with Novo Nordisk Insulin Delivery Devices, NovoFine®, NovoFine® Plus and/or NovoTwist® needles. Novo Nordisk cannot be held responsible for malfunctions occurring as a consequence of using NovoMix® 30 in combination with products that do not meet the same specifications or quality standards as NovoFine®, NovoFine® Plus and/or NovoTwist® needles

Do not use NovoMix® 30 if:

- You feel a hypoglycemic reaction (low blood sugar) coming on. (see '*What are possible side effects from using NovoMix® 30?*' for more about hypoglycemia).
- You are allergic (hypersensitive) to soluble insulin aspart, insulin aspart protamine crystals, metacresol or any of the other ingredients in this insulin. Look out for the signs of an allergic reaction. (see '*What are possible side effects from using NovoMix® 30?')*.
- In insulin infusion pumps.
- If the Penfill® cartridge in a Novo Nordisk Insulin Delivery Device containing the insulin is dropped, damaged or crushed; there is a risk of leakage of insulin.
- The insulin has not been stored correctly or if it has been frozen. (see *'How to store NovoMix® 30"*).
- The insulin is not uniformly white and cloudy when it is mixed.
- 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®, NovoFine® Plus and NovoTwist® 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.

As a precautionary measure, always carry a spare insulin cartridge/delivery system in case your Penfill® is lost or damaged.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NovoMix® 30. Talk about any health conditions or problems you may have, including if you:

- Have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands, your doctor may decide to alter your insulin dose.
- Drink alcohol (including wine and beer) your need for insulin may change as your blood sugar level may either rise or fall.
- Have an infection, fever or have had an operation you may need more insulin than usual.
- Suffer from diarrhea, vomiting or eat less than usual you may need less insulin than usual.

- Exercise more than usual or if you want to change your usual diet.
- Are ill: continue taking your insulin. Your need for insulin may change.
- Go abroad: travelling over time zones may affect your insulin needs and the timing of your injections. Consult your doctor if you are planning such travel.
- Are pregnant or planning a pregnancy or are breastfeeding please contact your doctor for advice.
- Drive or use tools or machines: watch for signs of a hypoglycemia. Your ability to concentrate or to react will be less during a hypoglycemic reaction. 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 hypoglycemic reaction coming on.

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

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.

Thiazolidinediones (class of oral antidiabetic drugs) used together with insulin may increase risk of oedema and heart failure. Inform your doctor as soon as possible if you experience localised swelling (oedema) or signs of heart failure such as unusual shortness of breath.

Other warnings you should know about:

Skin changes at the injection site

The injection site should be rotated to help prevent changes to the fatty tissue under the skin, such as skin thickening, skin shrinking or lumps under the skin. The insulin may not work very well if you inject into a lumpy, pitted, or thickened area (see 'How to take NovoMix®'). Tell your healthcare professional if you notice any skin changes at the injection site. Tell your healthcare professional if you are currently injecting into these affected areas before you start injecting in a different area. A sudden change of site may result in hypoglycemia. Your healthcare professional may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

The following may interact with NovoMix® 30:
Some medicines affect your blood sugar level and this may mean that your insulin dose has to change. Listed below are the most common medicines, which may affect your insulin treatment. Tell your doctor, Diabetes Nurse Educator or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. In particular, you should tell your doctor if you are using any medicine as mentioned below that affects your blood sugar level.

If you take any of the medicines below, your blood sugar level may fall (hypoglycemia):
- Other medicines for the treatment of diabetes
- Monoamine oxidase inhibitors (MAOI) (used to treat depression)
- Beta-blockers (used to treat high blood pressure)
- Angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure)

- Salicylates (used to relieve pain and lower fever)
- Anabolic steroids (such as testosterone) Sulphonamides (used to treat infections)

If you take any of the medicines below, your blood sugar level may rise (hyperglycemia):
- Oral contraceptives (birth control pills)
- Thiazides (used to treat high blood pressure or excessive fluid retention)
- Glucocorticoids (such as 'cortisone' used to treat inflammation)
- Thyroid hormones (used to treat thyroid gland disorders)
- Sympathomimetics (such as epinephrine [adrenaline], or salbutamol, terbutaline used to treat asthma)
- Growth hormone (medicine for stimulation of skeletal and somatic growth and pronounced influence on the body's metabolic processes)
- Danazol (medicine acting on ovulation)

Octreotide and lanreotide (used for treatment of acromegaly, a rare hormonal disorder that usually occurs in middle-aged adults, caused by the pituitary gland producing excess growth hormone) may either increase or decrease your blood sugar level.

Beta-blockers (used to treat high blood pressure) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycemia.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take NovoMix® 30:
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 *'What are possible side effects from using NovoMix® 30?')*. The best places to give yourself an injection are: the front of your thighs; the front of your waist (abdomen); the upper arm. Your insulin will work more quickly if you inject into the front of your waist.

You should always measure your blood glucose regularly.

Talk about your insulin needs with your doctor and Diabetes Nurse Educator. Do not change your insulin unless your doctor tells you to. Follow their advice carefully. This leaflet is a general guide only.
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.

Before using NovoMix® 30:
- Check the label to make sure you have the right type of insulin.
- 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.

- Always use a new needle for each injection to prevent contamination.
- Do not share your NovoMix® 30 Penfill® in a Novo Nordisk Insulin Delivery Device with another person, even if the needle is changed. Do not reuse or share needles with another person including family members. You may give another person an infection or get an infection from them.

Resuspending the insulin

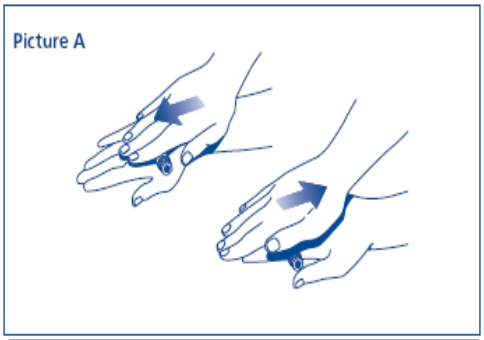
Check that there are at least 12 units of insulin left in the cartridge to allow even resuspension. If there are less than 12 units left, use a new cartridge.

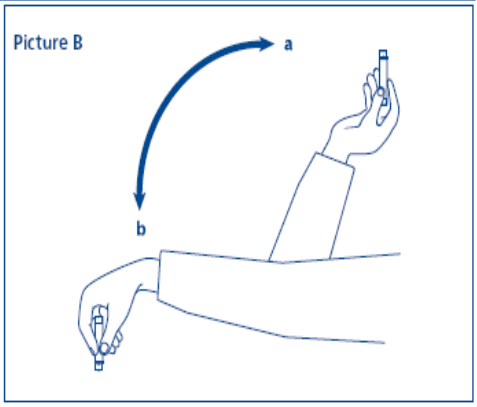
Every time you use a new NovoMix® 30 Penfill® (before you put the cartridge into the insulin delivery system):

- Let the insulin reach room temperature before you use it. This makes it easier to resuspend. Roll the cartridge between your palms ten times – it is important that the cartridge is kept horizontal (see picture **A**).
- Move the cartridge up and down between positions **a** and **b** (see picture **B**) 10 times so that the glass ball moves from one end of the cartridge to the other.
- Repeat the rolling and moving procedures (see picture **A** and **B**) until the liquid appears uniformly white and cloudy. Do not use the cartridge if the resuspended insulin does not look uniformly white and cloudy.
- Complete the other stages of injection without delay.

For all subsequent injections:

- Move the insulin delivery system with the cartridge inside it, up and down between **a** and **b** (see picture **B**) at least ten times until the liquid appears uniformly white and cloudy.
- Complete the other stages of injection without delay.





How to inject this insulin

- Inject the insulin under the skin. Use the injection technique advised by your doctor or Diabetes Nurse Educator and as described in your Novo Nordisk Insulin Delivery Device manual.
- Keep the needle under your skin for at least 6 seconds. Keep the push-button fully depressed until the needle has been withdrawn. This will ensure correct delivery and limit possible flow of blood into the needle or insulin reservoir.
- After each injection be sure to remove and discard the needle and store NovoMix® 30 without the needle attached. Otherwise, insulin may leak out which can cause inaccurate dosing.

Overdose:

You get a hypoglycemia 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.

The warning signs of a hypoglycemia 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 hypoglycemia 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 hypoglycemia that makes you pass out, or if you get a lot of hypoglycemias, 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 hypoglycemia in order to avoid getting more.

Causes of a hyperglycemia:
You get a hyperglycemia if your blood sugar gets too high.
This might happen:
- If you forget to take insulin.
- If you repeatedly take less insulin than you need.
- If you eat more than usual.
- If you exercise less than usual.

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.

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.

If you think you, or a person you are caring for, have taken too much NovoMix® 30, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using NovoMix® 30?

These are not all the possible side effects you may feel when taking NovoMix® 30. If you experience any side effects not listed here, contact your healthcare professional.

The most common side effect is low blood sugar (hypoglycemia). See the advice in *'How to take NovoMix® 30'*.

Less common (1 to 10 users in 1000):
Signs of allergy
Hives and rash may occur.

Seek medical advice immediately:
- If the above signs of allergy appear 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 generalized allergic reaction). See also the warning in *'Do not use NovoMix® 30 if'.*

Vision problems
When you first start your insulin treatment it may disturb your vision, but the disturbance is usually temporary.

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

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.

Rare (less than 1 user in 10,000)

Painful neuropathy (pain due to nerve damage)
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.

Frequency Not known

Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). See *"Other warnings you should know about"*.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
LESS COMMON (1 to 10 users in 1000)			
Signs of allergy: hives and rash		√	√
Vision problems	√		√
Skin changes where you inject your insulin injection (lipodystrophy)		√	√
Swelling around your joints	√		√
Blood glucose levels improve very fast and worsening of diabetic retinopathy		√	√
RARELY REPORTED (less than 1 user in 10,000)			
Blood glucose levels improve very fast and nerve related pain (painful neuropathy)		√	√
UNKNOWN			
Cutaneous Amyloidosis: lumps under skin		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

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

NovoMix® 30 that is being used or is about to be should not 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 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.

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

Keep out of reach and sight of children.

What NovoMix® 30 looks like and package content
NovoMix® 30 Penfill® comes as a white suspension in packages of 5 cartridges of 3 mL per carton.

1 Penfill® cartridge contains 3 mL of insulin aspart equivalent to 300 U.

If you want more information about NovoMix® 30:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.novonordisk.ca, or by calling 1-800-465-4334.

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