

PRODUCT MONOGRAPH

Schedule D

NovoMix[®] 30

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

Suspension for Injection

100 Units/mL

Professed

Antidiabetic Agent

Novo Nordisk Canada Inc.
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Control No. 145855

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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

- Hypoglycaemia is the most common adverse effect of insulin products. As with all insulin products the timing of hypoglycaemia 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 hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma or even death. (See ENDOCRINE AND METABOLISM – HYPOGLYCEMIA)
- Any transfer of insulin products should be made cautiously and only under medical supervision. (See WARNINGS AND PRECAUTIONS)
- 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 to 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).

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; patients with diabetes may also require a longer-acting insulin to maintain adequate glucose control.

Hypokalemia is among the potential clinical adverse effect associated with the use of all insulin therapies. This potential clinical adverse effect may be relevant in patients who are on potassium lowering drugs or losing potassium through other means (e.g. diarrhoea).

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.

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 TREATMENT OF OVERDOSAGE*).

Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia.

Concomitant illness, especially infections and feverish conditions, usually increase the patient's insulin requirement. Concomitant diseases in the kidney, liver or affecting the adrenal, pituitary or thyroid gland can require changes in the insulin dose.

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 or, in extreme circumstances, even death which can occur without recognizable symptoms.

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

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 hyperglycaemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

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

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 may help to reduce or prevent these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of NovoMix® 30.

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

Immune responses can occur in response to insulin. This may be associated with elevated IgG levels, however this does not appear to affect HbA1c.

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.

Carcinogenesis and Mutagenesis

See *PART II: Scientific Information – Toxicology*.

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.

Sexual Function/Reproduction

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.

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 (> 65 years of age): 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.

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 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).

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				
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%
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%

	NovoMix® 30		BHI 30	
	N	(%)	N	(%)
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%		
Hyperglycaemia	1	<1%	3	3%
Hypoglycemia	1	<1%	2	2%
Oedema leg				2%
Cardiovascular Disorders, General				
Hypertension	16	16%	14	14%

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

	NovoMix® 30		BHI 30	
	N	(%)	N	(%)
Erythrocytes abnormal Anaemia Secondary Terms Injury accidental	2	2%	3	3%
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

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 ≤ 1/1,000).
- 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 ≤ 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 ≤ 1/1,000).
- 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 ≤ 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).

DRUG INTERACTIONS

Overview

As with insulin in general, concomitant use of other drugs may influence insulin requirements.

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).

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-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 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.

DOSAGE AND ADMINISTRATION

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.

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.

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. 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.

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.

HYPOGLYCEMIA AND 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 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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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).

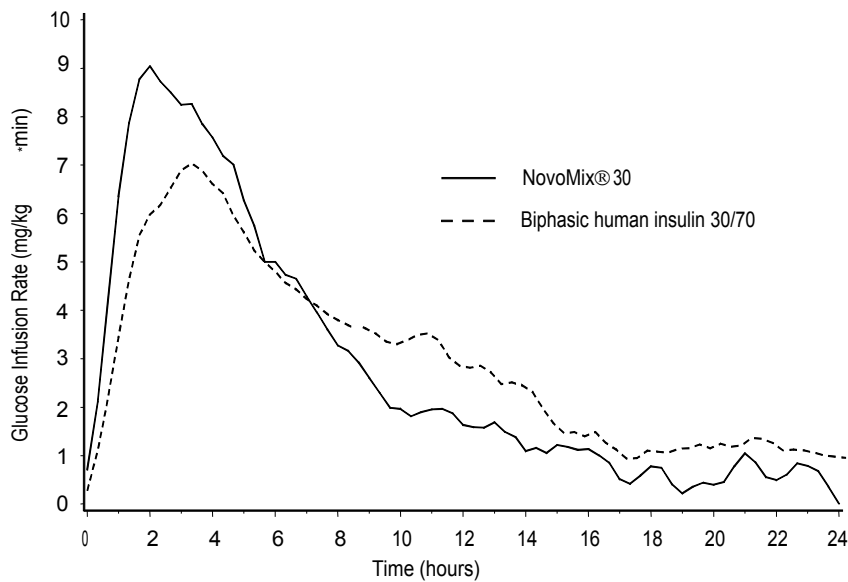


Figure 1: Pharmacodynamic activity profile of NovoMix® 30 and biphasic human insulin 30/70 in healthy subjects (ANA-033)

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.

**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.*

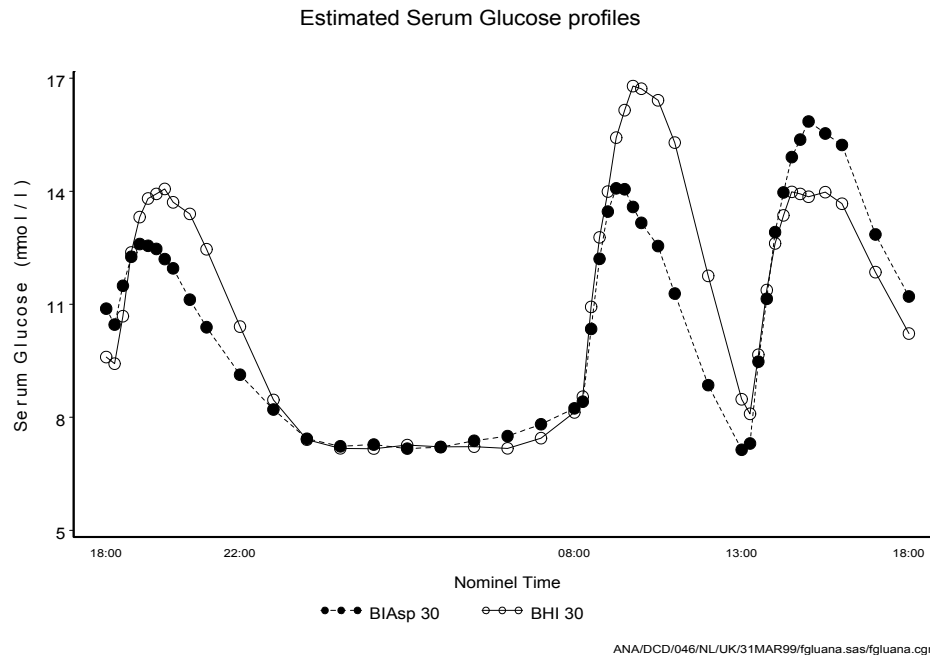


Figure 2: Estimated serum glucose levels following twice daily injection (immediately before breakfast and dinner) of NovoMix[®] 30 (BIAsp 30) or biphasic human insulin (BHI 30) in 13 patients with Type 2 diabetes (ANA-046).

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, $p < 0.001$). 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

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

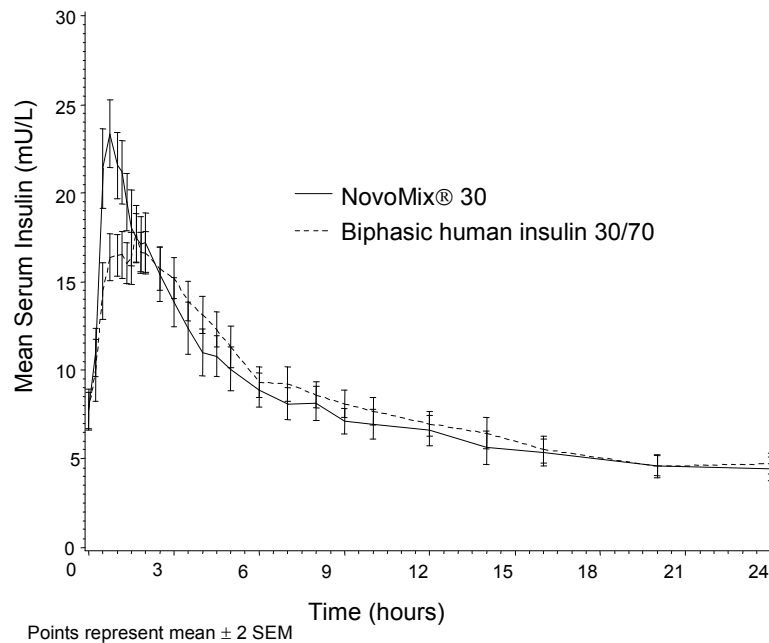


Figure 3: Mean serum insulin concentration following a single subcutaneous dose (0.2U/kg body weight) of NovoMix[®] 30 (solid line) and biphasic human insulin 30/70 (hatched line) in healthy subjects.

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°C and 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.

SPECIAL HANDLING INSTRUCTIONS

Penfill®: 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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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

NovoMix® 30 Penfill® cartridges are designed for use with Novo Nordisk Insulin Delivery Devices, NovoFine® and NovoTwist® needles.

1 mL of the solution contains 100 Units of soluble insulin aspart and protamine-cystallised insulin aspart in the 30/70 ratio (equivalent to 3.5 mg).

Pack sizes include 1 x 3 mL, 5 x 3 mL, and 10 x 3 mL.

Non-medicinal ingredients : 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.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Insulin Aspart

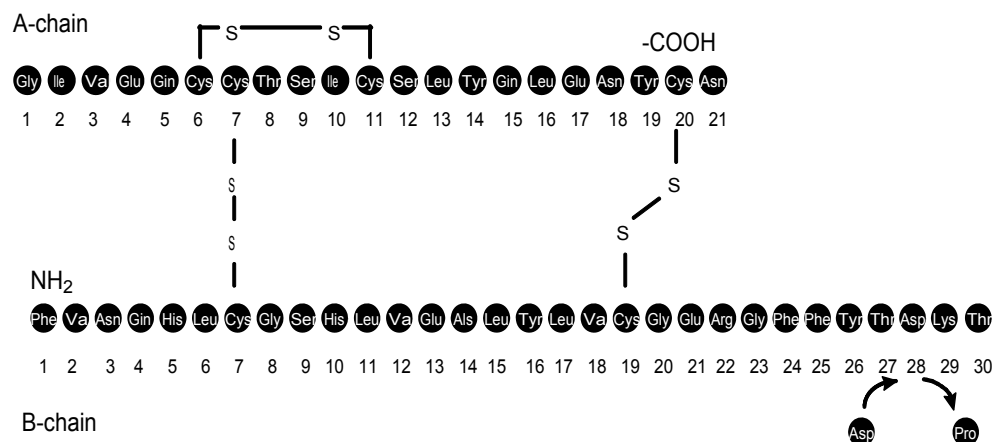
Chemical name: B28 asp regular human insulin analogue

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

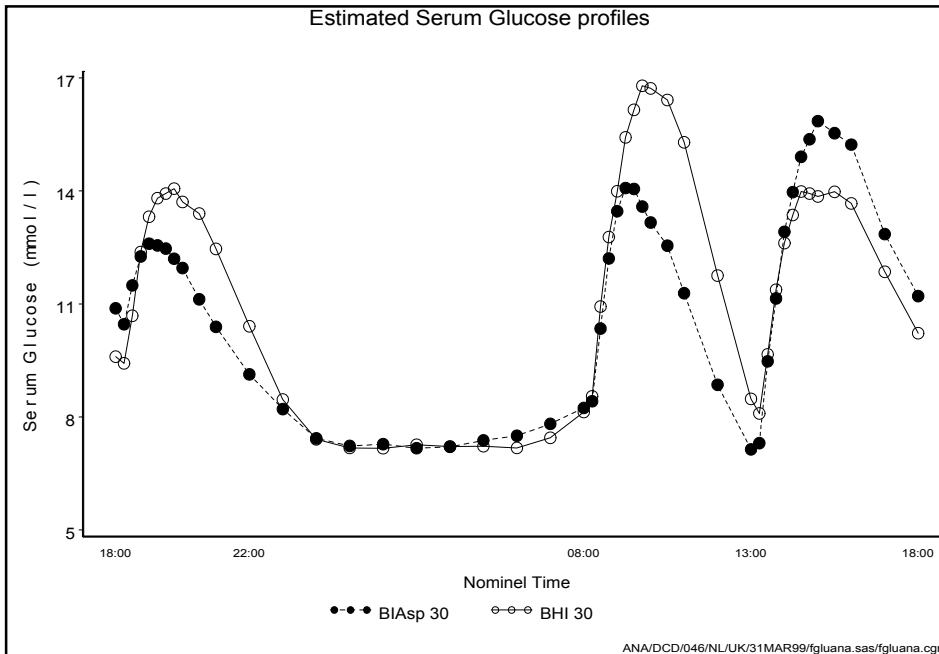


Figure 2: Estimated serum glucose levels following twice daily injection (immediately before breakfast and dinner) of NovoMix® 30 (BIAsp 30) or biphasic human insulin (BHI 30) in 13 patients with Type 2 diabetes.

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 glycaemic 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 glycaemic control did not increase the risk of hypoglycaemia. 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, glycaemic control, as measured by HbA_{1c}, was similar in the two groups.

With similar levels of glycaemic control (as assessed by HbA_{1c}), the number and rate of hypoglycaemic 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 hypoglycaemia than those receiving Novolin®ge 30/70 and during the last six months of the study, no patients treated with NovoMix® 30 experienced major hypoglycaemia.

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 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, $p < 0.001$). 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[®] 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 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) 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 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 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 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	1,10 or 100 U/kg IV,	No effects

Test	Insulin Aspart/ Human Insulin(HI)	Results
Performance, mice	HI 100 IU/kg IV	
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
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

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.

Species, Strain, Route	(M+F) Animals per group	Doses U/kg	Results
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 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	Hypoglycemia, increased food and water consumption and weight gain. Excess of mammary tumors in high dose

Species	Strain	Number of groups and size	Dosing Method	Duration (Weeks)	Dose level (U/kg/day)	Results
					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.	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.

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