

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

NovoRapid®

Insulin Aspart

Solution for Injection, 100 Units/mL, Subcutaneous Injection

Professed Standard

Anti-diabetic Agent

ATC code: A10AB05

fast-acting

Novo Nordisk Canada Inc.
101-2476 Argentia Road
Mississauga, Ontario
L5N 6M1 Canada

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RECENT MAJOR LABEL CHANGES

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

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

NovoRapid® (insulin aspart) is indicated for:

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

NovoRapid® should normally be used in regimens together with an intermediate or long-acting insulin.

NovoRapid® (10 mL vials) may also be used for continuous subcutaneous insulin infusion (CSII) in pump systems which are licensed in Canada for insulin infusion.

1.1 Pediatrics

Pediatrics (2-17 years of age): Evidence from clinical studies and experience suggests that use in the pediatric population is not associated with any differences in safety or effectiveness. Please see CLINICAL PHARMACOLOGY.

1.2 Geriatrics

Geriatrics (> 65 years of age): There was no clinically relevant difference in the pharmacokinetics and pharmacodynamics of NovoRapid® between elderly and younger subjects. Please see WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY.

2 CONTRAINDICATIONS

NovoRapid® is contraindicated in:

- During episodes of hypoglycemia;
- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 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. Glucose monitoring shall be performed for all patients with diabetes mellitus treated with insulins. (see HYPOGLYCEMIA, HYPERGLYCEMIA AND OVERDOSAGE)
- Uncorrected hypoglycemic or hyperglycemic 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)
- Some insulin products are short-acting insulin and are known for their rapid onset and short duration of action. The injection of such insulin products should immediately be followed by a meal (within 5-10 minutes or given immediately after

the meal. (see DOSAGE AND ADMINISTRATION)

- Short-acting insulin should be combined with a longer-acting insulin or insulin infusion pump therapy to maintain adequate glucose control. (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)
- Insulin products shall not be used if it is not water-clear and colourless or if it has formed a deposit of solid particles on the wall of the vial or cartridge. (see DOSAGE AND ADMINISTRATION)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Patients being initiated on insulin can be started on NovoRapid® in the same manner as they would be on animal-source or human insulin.
- Changes for patients being transferred from other insulin to NovoRapid® should be made as directed by a physician.
- In clinical trials, patients were transferred on a unit to unit basis from Novolin®ge Toronto to NovoRapid®. 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, NovoRapid® 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, NovoRapid® may be given immediately after the meal.

Dosage of NovoRapid® 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 meal-related treatment, 50-70% of this requirement may be provided by NovoRapid® and the remainder provided by an intermediate-acting or long-acting insulin.

The dosing of NovoRapid® should be regularly 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

NovoRapid® (insulin aspart) is administered subcutaneously by injection in the abdominal wall, the thigh, the upper arm, the deltoid region or the gluteal region. 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 sections ADVERSE REACTIONS and WARNINGS AND PRECAUTIONS). NovoRapid® retains its more rapid onset and shorter duration of action irrespective of the injection site used (abdomen, thigh, upper arm). As with all insulins, the duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

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

prior to administration, whenever solution and container permit. Never use NovoRapid® if it has become viscous (thickened) or cloudy; use it only if it is water-clear and colourless. NovoRapid® should not be used after its expiration date.

Mixing of Insulins

NovoRapid® can only be mixed with NPH (Neutral Protamine Hagedorn) insulin in a syringe for subcutaneous use. When NovoRapid® is mixed with NPH insulin, NovoRapid® should be drawn into the syringe first, and the mixture should be injected immediately after mixing. Insulin mixtures should not be administered intravenously or used with a subcutaneous insulin infusion pump. NovoRapid® should not be mixed with long-acting insulin analogue. The effect of mixing NovoRapid® with either animal-source insulins, or human insulin preparations produced by other manufacturers have not been studied. This practice is not recommended.

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.

NovoRapid® (10 mL vial) may be used for Continuous Subcutaneous Insulin Infusion (CSII) in pump systems licensed for insulin infusion. Patients using CSII should be comprehensively instructed in the use of the pump system. The infusion and reservoir set should be changed according to the pump manufacturer's instructions. Patients administering NovoRapid® by CSII must have an alternate insulin delivery device available in case of pump system failure.

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.

As a precautionary measure, patients should carry a spare syringe and extra insulin in case the insulin delivery device is lost or damaged.

5 OVERDOSAGE

Excess insulin administration may cause hypoglycemia and, particularly when given intravenously, hypokalemia. 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. Hypokalemia must be corrected appropriately.

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 recognise 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 | Solution for injection, 100 Units/mL | disodium phosphate dihydrate, glycerol, metacresol, phenol, sodium chloride, water for injection and zinc chloride solution. Sodium hydroxide 2N and/or hydrochloric acid may be added to adjust the pH. |

NovoRapid® (insulin aspart) is available in 10 mL vials, in 3 mL Penfill® cartridges and NovoRapid® FlexTouch® disposable pens.

NovoRapid® Penfill® cartridges are designed for use with Novo Nordisk Insulin Delivery Devices, NovoFine®, NovoFine® Plus and NovoTwist® needles. NovoRapid® FlexTouch® (pre-filled disposable pens) is specially designed for use with NovoFine®, NovoFine® Plus and NovoTwist® needles.

1 mL of the solution contains 100 Units of insulin aspart (equivalent to 3.5 mg).

Pack size for vial is 1 x 10 mL.

Pack sizes for all other presentations include 1 x 3 mL and 5 x 3 mL.

Description

NovoRapid® (insulin aspart) is a unique human insulin analogue of rDNA origin that rapidly lowers blood glucose. NovoRapid® is homologous with regular human insulin with the exception of a substitution of the amino acid proline for aspartic acid in position B28. The substitution of the amino acid proline with aspartic acid at position B28 in NovoRapid® reduces the tendency to form hexamers as observed with regular human insulin. NovoRapid® is therefore more rapidly absorbed from the subcutaneous layer compared to regular human insulin. The insulin is derived from the fermentation of genetically modified yeast cells (recombinant DNA origin, *Saccharomyces cerevisiae*). The fermentation, isolation, conversion and purification of insulin aspart are equivalent to the procedures used for production of genetically engineered human insulin.

7 WARNINGS AND PRECAUTIONS

Please see SERIOUS WARNINGS AND PRECAUTIONS BOX

General

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

NovoRapid® 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 NovoRapid® should immediately be followed by a meal. As a result of the short duration of action of NovoRapid®, patients with diabetes may also require a longer-acting insulin to maintain adequate glucose control.

Thiazolidinediones (TZDs), alone or in combination with other anti-diabetic 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, (see WARNINGS AND PRECAUTIONS), information when the use of these drugs in combination with any insulin, including NovoRapid®, is contemplated.

Never Share a NovoRapid® FlexTouch®, Penfill® or a Novo Nordisk Insulin Delivery Device Between Patients.

NovoRapid® FlexTouch®, Penfill® or a Novo Nordisk Insulin Delivery Device should never be shared between patients, even if the needle is changed. Sharing poses a risk for transmission of blood-borne pathogens.

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 NovoRapid® and other insulin products.

Carcinogenesis and Mutagenesis

See NON-CLINICAL TOXICOLOGY

Driving and Operating Machinery

No studies on the effects on the ability to drive and use machines have been performed. Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Endocrine and Metabolism

Hypoglycemia

As with other insulins, hypoglycemia is the most common adverse effect of insulin therapy, including NovoRapid®. Such reactions following treatment with NovoRapid® are mostly mild and easily managed. While the frequency of hypoglycemia observed in clinical trials is similar to that observed with regular human insulin, clinical trials in patients with type 1 diabetes have

demonstrated a reduced risk of nocturnal hypoglycemia with insulin aspart compared with soluble human insulin. The risk of daytime hypoglycemia was not significantly increased

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of NovoRapid®. 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 long-standing diabetes. Hypoglycemia may occur if the insulin dose is too high in relation to the insulin requirement. (see ADVERSE REACTIONS, Hypoglycemia and OVERDOSAGE)

Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia. Care should be taken, especially in children, to match insulin doses (especially in basal-bolus regimens) with food intake, physical activities and current blood glucose level in order to minimise the risk of hypoglycaemia.

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. 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 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 NovoRapid®, 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, patients receiving intravenously administered insulin, or patients losing potassium through other means (e.g., diarrhea)]. (see ADVERSE REACTIONS)

Hepatic/Biliary/Pancreatic

The pharmacokinetics of NovoRapid® did not change in patients with mild (Mean Child Pugh Score: 5.7), moderate (Mean Child Pugh Score: 7.3) or severe (Mean Child Pugh Score: 10.2) hepatic impairment as compared to subjects with normal hepatic function (Mean Child Pugh Score: 0). As with other insulins, NovoRapid® requirement may need to be adjusted in patients with hepatic impairment.

A single dose pharmacokinetic study of insulin aspart was performed in 24 non-diabetic subjects with hepatic function ranging from normal to severely impaired. In patients with hepatic impairment absorption rate was decreased and more variable, resulting in delayed t_{max} from about 50 minutes in subjects with normal hepatic function to about 85 minutes in patients with moderate and severe hepatic impairment. AUC, C_{max} and CL/F were similar in patients with reduced hepatic function compared with subjects with normal hepatic function.

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 NovoRapid®. Localized reactions and generalized myalgias have been reported with injected metacresol, which is an excipient in NovoRapid®. (see Skin and subcutaneous tissue disorders)

Systemic Allergic Reaction

Systemic allergic reactions have not been reported during the clinical development of NovoRapid®. Systemic allergic reactions have rarely occurred with NovoRapid® 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.

In the clinical development program, insulin aspart-specific, regular human insulin-specific and cross reactive antibodies were analyzed. Antibody production was monitored in 665 patients for 12 months. After a transient statistically significant increase in cross-reacting antibodies from baseline to 3 months for NovoRapid® compared to human insulin, cross-reacting antibody

levels returned to baseline levels in the NovoRapid® group and were not different from the human insulin group. No adverse effects could be attributed to patients producing cross-reactive antibodies as compared to those who did not. There was no correlation between the extent of antibody formation and the insulin dose needed, level of glycemic control attained or adverse event reporting after 12 months treatment. No systemic allergic reactions were observed.

In a clinical study on the use of NovoRapid® (n=157) during pregnancy in patients with type 1 diabetes, mean levels of antibodies specific to NovoRapid® were low (<3%). Variability between patients was up to 14% for NovoRapid®. The majority of antibodies were cross-reacting. There was no observable increase in antibodies with NovoRapid® treatment from baseline to the end of the third trimester.

Similar observations were found in cord blood. Mean levels of antibodies specific to NovoRapid® were low (<1%). The majority of insulin antibodies were cross-reacting, and variability between patients was up to 17% for NovoRapid® specific antibodies. Levels of antibodies in cord blood seemed to correlate with maternal antibodies which are consistent with a transfer of maternal cross-reacting insulin antibodies across the placenta. The same pattern was observed for NovoRapid® specific antibodies.

In a clinical trial including 14 women with gestational diabetes assigned to treatment with NovoRapid® mean levels of antibodies specific to NovoRapid® remained relatively low (less than 0.5% binding).

See also WARNING AND PRECAUTIONS, Sexual Health Function/Reproduction and Special Populations, Pregnant Women, ADVERSE REACTIONS, Clinical Trial Adverse Reactions, Pregnancy clinical trials; and Part II, SCIENTIFIC INFORMATION, CLINICAL TRIALS, type 1 diabetes.

Mixing of insulins: Mixing of an insulin formulation with another insulin formulation may change the pharmacokinetic and/or pharmacodynamic profile of action of the combined mixture in an unpredictable matter (see DOSAGE AND ADMINISTRATION).

Pharmacodynamic trials conducted in pigs showed bioequivalence between separate injections of NovoRapid®. These included neutral protamine regular human insulin, a mix of NovoRapid® and neutral protamine regular human insulin when injected 5 minutes after mixing.

Monitoring and Laboratory Tests

As with all insulin therapy, the need for regular blood glucose self-monitoring should be considered when using NovoRapid® to obtain optimal glycemic control. Periodic measurement of glycated hemoglobin is recommended for the monitoring of long-term glycemic control. If a patient is pregnant, 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

The pharmacokinetics of NovoRapid® did not change in patients with mild (mean Cl_{cr} 60.0 mL min^{-1}), moderate (mean Cl_{cr} : 35.7 mL min^{-1}) and severe (mean Cl_{cr} : 23.5 mL min^{-1}) renal impairment as compared to patient with normal renal function (Cl_{cr} : > 99.8 mL min^{-1}). The degree of renal impairment does not affect the pharmacokinetics variable of NovoRapid®. As

with other insulins, NovoRapid® requirement may be reduced in patients with renal impairment. NovoRapid® requirement may need to be adjusted in patients with severe renal impairment.

A single dose pharmacokinetic study of insulin aspart in 18 subjects with type 1 diabetes and with renal function ranging from normal to severely impaired was performed. No apparent effect of creatinine clearance values on AUC, C_{max} , CL/F and t_{max} of insulin aspart was found. Data were limited in patients with moderate and severe renal impairment. Patients with renal failure necessitating dialysis treatment were not investigated.

Reproductive Health: Female and Male Potential

Function

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

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.

Skin and subcutaneous tissue disorders

Subcutaneous administration of insulin products, including Novorapid® 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

Congenital anomalies are 3-4 times more prevalent in diabetic pregnancy than in non-diabetic pregnancies and with a two-fold higher mortality from major cardiovascular anomalies.

In a clinical trial of 157 pregnant women with type 1 diabetes treated with NovoRapid® 10 congenital malformations were reported in 9 (5.7%) patients treated with NovoRapid®. Cardiac

anomalies were reported (n=7), mainly septal defects (n=4). Additional reports in offspring of patients treated with NovoRapid® were one each of central nervous system anomaly, ankyloglossia and fetal disorders.

Of the women who received NovoRapid®, fetal exposure throughout the entire pregnancy occurred in 44 women. One child exposed to NovoRapid® had an anomaly neck edema resulting in fetal loss.

In a clinical trial of 14 women with gestational diabetes who received treatment with NovoRapid®, two infants had abnormal findings and all findings were felt to be unrelated to the treatment.

See also WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women; ADVERSE REACTIONS, Clinical Trial Adverse Reactions, Pregnancy clinical trials; and Part II, SCIENTIFIC INFORMATION, CLINICAL TRIALS, type 1 diabetes.

NovoRapid® can be used in pregnant women with type 1 diabetes if clinically indicated. It is essential for patients with type 1 diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements usually decrease during the first trimester and increase during the second and third trimesters. Patients should be advised to inform their health care professional if they are pregnant or are contemplating pregnancy. Careful monitoring of glucose control is essential in these patients.

A study was conducted in 157 pregnant women with type 1 diabetes treated with NovoRapid®. Two-thirds (n=113) of the enrolled patients were already pregnant when they entered the study. Because only one-third (n=44) of the patients were enrolled before conception, the sample size was not large enough to evaluate the risk of congenital malformations. A1C was evaluated during the study as well as the incidence of hypoglycemia. (see also, [Clinical Trial Adverse Drug Reactions](#), Pregnancy clinical trials and Part II, SCIENTIFIC INFORMATION, CLINICAL TRIALS, type 1 diabetes)

Reproduction studies have been performed in rats and rabbits at doses up to 16-32 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to NovoRapid®.

7.1.2 Breast-feeding

It is unknown if NovoRapid® is excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk. Patients with diabetes who are lactating may require adjustments in insulin dose, meal plan or both.

7.1.3 Pediatrics

(2-17 years of age)

The pharmacokinetic properties of NovoRapid® (insulin aspart injection) and regular human insulin were investigated in 18 children (6-12 years, n=9) and adolescents 13-17 years, n=9) with type 1 diabetes. The relative difference in pharmacokinetics and pharmacodynamics in type 1 diabetic children and adolescents between NovoRapid® and regular human insulin correlated well with those in healthy adult subjects and type 1 diabetic adults.

The efficacy and safety of NovoRapid® were compared to regular human insulin, both supplemented with NPH insulin, in a 24-week crossover (two 12-week treatments), randomized trial in children (age 2-6, n=25) with type 1 diabetes. NovoRapid®, injected either shortly before meal or immediately after a meal, produced the same effects with respect to postprandial blood glucose control (p=0.5180) and to overall glycemic control (as measured by A1C levels, $7.7 \pm 0.23\%$ vs $7.56 \pm 0.25\%$, 0.111 (95% CI -0.113:0.336) as regular human insulin, injected 30 minutes before a meal. The safety profile was comparable to that of regular human insulin and did not appear to differ from that of NovoRapid® in adults with type 1 diabetes. In addition, as compared to regular human insulin, NovoRapid® did not increase the frequency and risk of hypoglycemia [RR 1.06 (95% CI: 0.96-1.17; p=0.225)].

In another trial, the efficacy and safety of NovoRapid® were compared to insulin lispro and regular human insulin in a 24-week, randomized, open label study in 378 children (6-18 years of age) with type 1 diabetes. NPH insulin was administered as basal insulin. Baseline means A1C values for NovoRapid®, lispro and regular human insulin were $8.3 \pm 1.2\%$, $8.4\% \pm 1.2\%$ and $8.3 \pm 1.2\%$, respectively. At the end of the study, patients had mean A1C values of $8.4 \pm 1.4\%$, $8.2 \pm 1.2\%$ and $8.3 \pm 1.4\%$, respectively. The changes from baseline were not significantly different among the groups. NovoRapid® demonstrated similar, postprandial, blood glucose levels as lispro. The blood glucose levels after lunch and dinner decreased significantly with NovoRapid® than with regular human insulin (lunch: 10.2 ± 4.5 mmol/L vs. 11.2 ± 4.7 mmol/L, respectively; p=0.009; dinner: 10.5 ± 4.4 mmol/L vs. 11.6 ± 4.8 mmol/L, respectively; p=0.003. Furthermore, NovoRapid® did not increase the risk of hypoglycemia and had a safety profile comparable to both regular human insulin and lispro.

7.1.4 Geriatrics

PK/PD study comparing insulin aspart with soluble human insulin was performed in 19 elderly patients with type 2 diabetes. The relative differences in the pharmacodynamic properties between insulin aspart and human insulin in elderly were consistent with those seen in healthy subjects and in younger patients with diabetes. However, careful glucose monitoring and individual dose adjustments of insulin, including insulin aspart, may be necessary in elderly patients. (see CLINICAL PHARMACOLOGY)

In the clinical development program, 226 patients aged 50 years and older (including 35 patients above the age of 65) were treated with NovoRapid® for up to 6 months. No differences in dose, efficacy or adverse events were observed between these patients and younger population.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse reactions observed in patients using NovoRapid® are mainly due to the pharmacologic effect of insulin. The most frequently seen undesirable effect in insulin-treated patients is change in blood glucose levels. From clinical investigations, it is known that major hypoglycemia, defined as need for assistance in treatment, is common (>1/10) in well-controlled patients. Based on post-marketing experience adverse events including hypoglycemia are rare (>1/10,000 and <1/1000) during use of Novo Nordisk human insulin products.

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.

The safety profile of NovoRapid® observed in clinical trials is similar to the safety profile reported for Novo Nordisk human insulin products.

Frequencies of adverse drug reactions from clinical trials, which by an overall judgement are considered related to NovoRapid® are listed below. The frequencies are defined as: Uncommon (>1/1000, <1/100) and rare (>1/10,000, <1/1000). Isolated spontaneous cases are presented as very rare defined as (<1/10,000).

Immune system disorders:

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

Very Rare (>1/10,000, <1/1000): 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.

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 glycaemic control may be associated with worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders:

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

Lipodystrophy (including lipohypertrophy, lipoatrophy) may occur at the injection site as a consequence of failure to rotate injection sites within an area. Continuous rotation of the injection site within the particular injection area reduces the risk of developing these reactions.

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.

General disorders and administration site conditions:

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

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

Pregnancy Clinical Trials

In a clinical trial comparing safety and efficacy of NovoRapid® to insulin human in the treatment of pregnant women with type 1 diabetes (322 exposed pregnancies 157 to insulin aspart 165 to human insulin) the adverse event profiles were similar in patients receiving NovoRapid® and those receiving regular human insulin with respect to incidence and severity. Most adverse events were mild or moderate in severity. With the exception of obstetric complications, the adverse event profile was similar in patients during pregnancy and outside pregnancy. There were no differences in the incidence of obstetric complications between treatment groups.

Maternal Serious Adverse Events with possible or probable relationship to trial drug

Serious adverse events with possible or probable relation to trial drug were reported with NovoRapid® or regular human insulin in >1% of subjects: hypoglycemia, inadequate control of diabetes, hypoglycemic coma.

The following maternal serious adverse events with possible or probable relationship to trial drug were reported at an incidence of <1% for NovoRapid®: spontaneous abortion, missed abortion and cesarean section. (see also WARNINGS AND PRECAUTIONS, Functions/reproduction and Special populations; Pregnant Women; and Part II, SCIENTIFIC INFORMATION, CLINICAL TRIALS, type 1 diabetes)

8.3 Less Common Clinical Trial Adverse Reactions

In addition, the following adverse events were reported at an incidence of <1% for NovoRapid® regardless of drug relationship. Breech presentation, complication of delivery, hyperemesis gravidarum, HELLP syndrome, premature labour, ketoacidosis, ketonuria, acute bronchitis, hepatitis C, tonsillitis, tracheitis, uterine atony, asthenia, generalized oedema, contusion, obstetric procedure complication.

No clinically relevant differences were observed for any of the laboratory assessments, vital signs, ECG, or urine albumin/creatinine.

In each treatment group (NovoRapid® and insulin human), 3 malformations resulted in fetal loss or death of the child. Serious adverse events were reported in 36% of children in the NovoRapid® group and 29% of children in the regular human insulin group, the child adverse events profile was similar to that normally seen in children of diabetic mothers 33.6% of children in the NovoRapid® group and 39.7% in the regular human insulin group experienced hypoglycemia leading to treatment (oral or intravenous glucose/dextrose or early feeding).

The most frequently reported adverse event with a frequency of over 1% in the clinical trial of 27 women with gestational diabetes the most commonly reported reaction was upper respiratory tract infection, as well as hypoglycemic reactions.

In the gestational pregnancy study 71% of women in the insulin aspart group and 69% of women in the regular human insulin group experienced a symptomatic hypoglycemic episode. No major hypoglycemic episodes were reported in this study.

Two infants in each group had abnormal findings; all findings were felt to be unrelated to the treatment. In the NovoRapid® group, one fetal death occurred *in utero* due to umbilical cord strangulation at week 40, and one small pneumothorax and tachypnea which resolved the following day.

8.5 Post-Market Adverse Reactions

Adverse Drug Event Overview for a Post-Marketing CSII Trial

A 4 month post-marketing study in 511 patients with type 1 and insulin-requiring type 2 diabetes mellitus was conducted as a preference trial to assess the treatment satisfaction of NovoRapid® and insulin lispro during CSII pump therapy. Adverse drug events were recorded when spontaneously reported by the patients in the study. The only adverse drug event reported at an incidence $\geq 1\%$ was upper respiratory tract infection (incidence of 1.3% in the NovoRapid® group).

Less Common Adverse Drug Events (<1%) in a Post-Marketing CSII Trial

In addition, the following adverse drug events were reported at an incidence of <1% for NovoRapid® or insulin lispro in this study (in more than 1 patient in each treatment group), regardless of drug relationship.

Gastrointestinal Disorders: vomiting, nausea

Infections and Infestations: viral infection, urinary tract infection, sinusitis, onychomycosis, nasopharyngitis, bronchitis

Metabolism and Nutrition Disorders: hypoglycemia, hyperglycemia, diabetic ketoacidosis

Musculoskeletal and Connective Tissue Disorders: pain in extremity, back pain, arthralgia

Nervous System Disorders: neuropathy

Respiratory, Thoracic and Mediastinal Disorders: nasal congestion

The following serious adverse events were reported in more than 1 patient but at an incidence of < 1% for NovoRapid® in Study 2190:

Metabolic and nutritional disorders: hypoglycemia (4 episodes) and diabetic ketoacidosis (2 episodes)

Hypoglycemia as an Adverse Drug Reaction in a Post-Marketing CSII Trial

The reporting of hypoglycemia was not a specific safety endpoint in this trial. Hypoglycemic episodes were recorded only if spontaneously reported by the subject as adverse drug reactions. Consequently, data on hypoglycemia is limited from this study. There were only 7 episodes of hypoglycemia reported during the four-month trial with over 500 patients. As such, the incidence of hypoglycemia was calculated to be <1% of the patients treated with either NovoRapid® or insulin lispro and does not reflect real-life occurrence of hypoglycemia in diabetes patients.

9 DRUG INTERACTIONS

Overview

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

9.4 Drug-Drug Interactions

The drugs listed below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

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

To avoid the risk of developing new or worsening heart failure, the use of TZDs in combination therapy with NovoRapid® 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.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

The effect of smoking on the pharmacokinetics and pharmacodynamics of NovoRapid® has not been studied. However, metabolic control was similar in smokers and non-smokers after 6 months treatment with NovoRapid® in the clinical development program.

The influence of obesity and/or subcutaneous fat thickness on the pharmacokinetics and glucodynamics of NovoRapid® has not been studied. Patients with a body mass index (BMI) up to 40kg/m² were treated with NovoRapid®. No difference was observed in efficacy and safety compared to leaner patients.

Patients should be informed about potential advantages and disadvantages of NovoRapid® (insulin aspart) 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 NovoRapid® to obtain optimal glycemic control.

Alcohol may intensify or reduce the hypoglycemic effect of insulin.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The primary activity of NovoRapid® is the regulation of glucose metabolism. Insulins, including NovoRapid®, bind to the insulin receptors on muscle and fat cells and lower blood glucose by facilitating the cellular uptake of glucose - and simultaneously inhibit the output of glucose from the liver.

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. NovoRapid® is equipotent to regular human insulin on a molar basis.

NovoRapid® produces a more rapid and more pronounced blood glucose lowering effect than regular human insulin, due to a faster absorption from the injection site.

When administered immediately before a meal, the effect of NovoRapid® more closely mimics normal physiological postprandial insulin release than regular human insulin used as replacement therapy. This effect leads to reduced postprandial variability in blood glucose concentration.

In patients with diabetes mellitus, postprandial blood glucose levels are identified as a predictor of A1C levels. Furthermore, postprandial glucose control is an independent risk factor for morbidity and mortality in diabetics. This has been demonstrated with regard to overall mortality and cardiovascular disease and death. Since cardiovascular disease is the most frequent cause of death in a diabetic population, control of postprandial glucose levels is now recognized as an important clinical endpoint of successful diabetic therapy.

Optimized metabolic control in diabetic patients effectively delays the onset and slows the progression of late diabetic complications. Optimized metabolic control, including glucose monitoring is therefore

10.2 Pharmacodynamics

NovoRapid® (insulin aspart) produces a more rapid and pronounced blood glucose regulating effect than regular human insulin, due to the fast onset of action.

When insulin aspart is injected subcutaneously, the onset of action occurs within 10-20 minutes of injection. The maximum effect is exerted between 1 and 3 hours after injection. The duration of action of NovoRapid® is 3-5 hours.

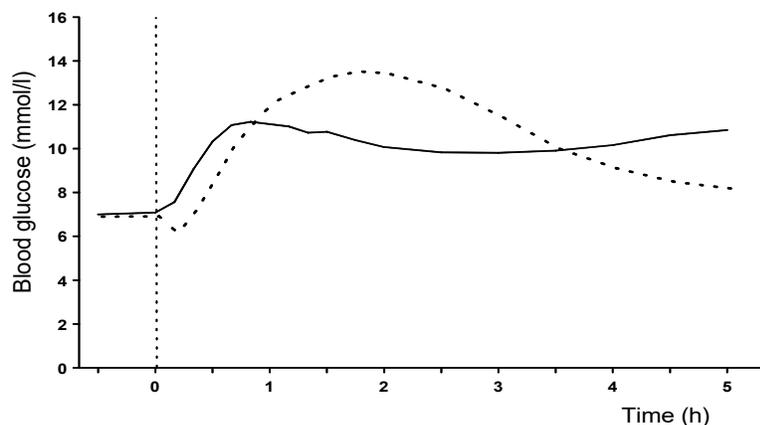


Figure 1: Mean blood glucose levels following a single pre-meal subcutaneous dose (0.15U/kg) of NovoRapid® injected immediately before a meal (solid line) or regular human insulin administered 30 minutes before a meal (hatched line) in 22 patients with type 1 diabetes.

The mean serum glucose profiles in the figure above show the superior postprandial glucose control obtained with NovoRapid® compared to human insulin during the first 4 hours post dosing. This was confirmed by the significantly lower postprandial glucose excursion (EXC) for NovoRapid® than for regular human insulin ($p = 0.015$).

Geriatrics (> 65 years of age):

A randomised, double-blind crossover PK/PD trial compared the pharmacodynamics and pharmacokinetics of a single 0.3 U/kg s.c. dose of insulin aspart (IAsp) and a single 0.3 U/kg s.c. dose of with soluble human insulin (HI) was performed in elderly patients with type 2 diabetes (19 patients aged 65-83 years, (mean age 70 years). The relative differences in the pharmacodynamic properties between insulin aspart and human insulin in elderly were consistent with those seen in healthy subjects and in younger patients with diabetes. However, no safety issues were raised, but careful glucose monitoring and individual dose adjustments of insulin, including insulin aspart, may be necessary in elderly patients.

Children and adolescents (2-17 years):

When given to children NovoRapid® showed similar long-term glucose control compared to soluble human insulin

10.3 Pharmacokinetics

In NovoRapid® substitution of the amino acid proline with aspartic acid at position B28 reduces the tendency to form hexamers as observed with soluble human insulin.

NovoRapid® is therefore more rapidly absorbed from the subcutaneous layer compared to soluble human insulin.

The time to maximum concentration is on average, half of that for soluble human insulin. A mean maximum plasma concentration of 492 ± 256 pmol/l was reached 40 (interquartile range: 30-40) minutes after a subcutaneous dose of 0.15 U/kg bodyweight in type 1 diabetic patients. The insulin concentrations returned to baseline about 4 to 6 hours after dose. The absorption rate was somewhat slower in type 2 diabetic patients, resulting in a lower C_{max} (352 ± 240 pmol/l)

and later t_{max} [60 (interquartile range: 50-90) minutes]. The intra-individual variability in time to maximum concentration is significantly less for NovoRapid® than for soluble human insulin, where the intra-individual variability in C_{max} for NovoRapid® is larger.

Reduced renal or hepatic function does not alter the pharmacokinetics of NovoRapid®.

Absorption

NovoRapid® (insulin aspart) has a faster absorption, a faster onset and a shorter duration of action than regular human insulin (see Fig. 1 and Fig. 2). The relative bioavailability of NovoRapid® to regular human insulin indicates that the two insulins are absorbed to a similar extent.

In clinical trials in healthy volunteers and type 1 diabetic patients, NovoRapid® consistently reached maximum serum concentration at least twice as fast as regular human insulin. The average median time to maximum serum concentration was 40-50 minutes for NovoRapid® versus 80-120 minutes for regular human insulin. The intra-individual variability in time to maximum concentration was significantly less for NovoRapid® than for regular human insulin.

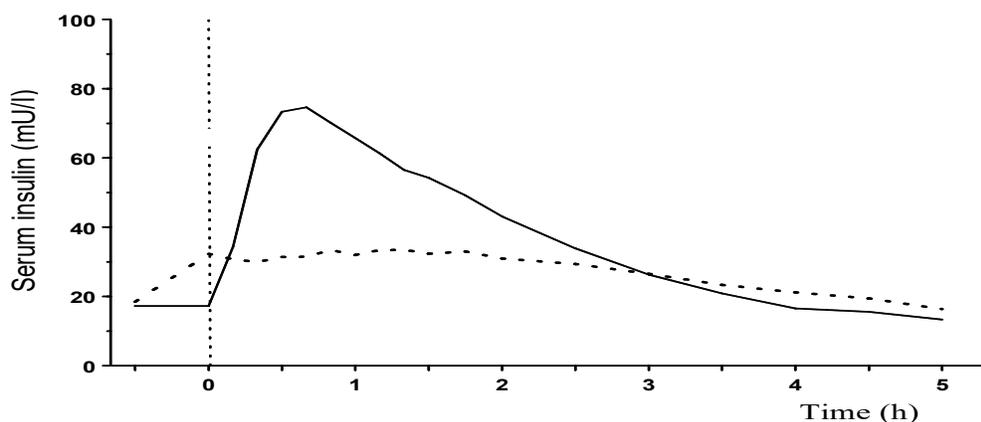


Figure 2: Mean serum insulin concentration following a single pre-meal subcutaneous dose (0.15U/kg body weight) of NovoRapid® injected immediately before a meal (solid line) or regular human insulin administered subcutaneously 30 minutes before a meal (hatched line) in 22 patients with type 1 diabetes.

The pharmacokinetics following a single 0.15 U/kg dose of NovoRapid® just before a standard meal or of regular human insulin 30 minutes before a standard meal were compared in type 1 diabetic patients (Fig. 2 above). NovoRapid® was rapidly absorbed after s.c. administration. There was a significant difference between C_{max} for NovoRapid® and regular human insulin (mean maximum concentrations 82.1 mU/l and 35.9 mU/l respectively).

The absorption rate was somewhat slower in type 2 diabetic patients, resulting in a lower C_{max} , 352 ± 240 pmol/l, and later t_{max} , 60 minutes.

In healthy subjects, the pharmacokinetic differences between NovoRapid® and regular human insulin, were maintained independent of the injection site (abdomen, thigh or deltoid).

When compared to regular human insulin on an equimolar basis, NovoRapid® produces significantly superior control of blood glucose following a meal as assessed by excursion of blood glucose during the first 4 hours after a meal (Fig. 1). When injected subcutaneously into

the abdomen, the onset of action will occur from 10 minutes after injection. The maximum effect is exerted between 1-3 hours after subcutaneous injection. The duration of action for NovoRapid® is 3-5 hours compared to 5-8 hours for regular human insulin. In this trial, patients were clamped from the evening before the trial product administration in order to obtain a blood glucose concentration of 5-8 mmol/l.

The effect of NovoRapid® given in a meal related regimen on 23-hour glucose control was studied in 104 type 1 diabetic patients. After 4 weeks of treatment, the instances of blood glucose levels outside the normal range (4-7 mmol/l or 72-126mg/dl) were significantly lower with NovoRapid® than with regular human insulin.

The extent of absorption (AUC) and $t_{\max(\text{ins})}$ for NovoRapid® were found to be independent of injection site when NovoRapid® was administered subcutaneously in the abdomen, deltoid, or thigh. However, $C_{\max(\text{ins})}$ was statistically significantly higher following injection into the abdomen relative to the thigh.

Distribution:

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

Metabolism:

Long-term metabolic control, assessed by A1C was studied in 882 type 1 diabetic patients in one trial and 1065 type 1 diabetic patients in another trial, on a meal-related insulin regimen. With NovoRapid®, significantly improved long-term metabolic control was obtained compared to regular human insulin after 6 months treatment, the values being $7.78 \pm 0.03\%$ for NovoRapid® and $7.93 \pm 0.05\%$ ($p < 0.01$) for regular human insulin in one trial and correspondingly $7.88 \pm 0.03\%$ and $8.00 \pm 0.04\%$ ($p < 0.02$) in the other trial. Furthermore, this improvement in glycemic control was achieved without increasing the risk of hypoglycemic events.

In 182 type 2 diabetic patients treated with NovoRapid® in a meal-related regimen for 6 months, the pharmacodynamic properties of NovoRapid® were shown to be not different than regular human insulin with respect to metabolic control as assessed by insulin dose (meal related and NPH).

The degradation products (metabolites) of NovoRapid® are assumed to be natural amino acids and peptides, which are subsequently incorporated into host proteins or metabolised, as is the case with human insulin. A number of cleavage (hydrolysis) sites on the human insulin molecule have been proposed; none of the insulin metabolites formed following cleavage are

active.

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. The rapid elimination of NovoRapid® is reflected in the return of NovoRapid® concentrations to pre-dosing levels within 4 hours after dosing.

Special Populations and Conditions

- **Pediatrics:** The pharmacokinetic properties of NovoRapid® (insulin aspart) and regular human insulin were investigated in 18 children (6-12 years, n=9) and adolescents (13-17 years, n=9) with type 1 diabetes. The relative difference in pharmacokinetics and pharmacodynamics in type 1 diabetic children and adolescents between NovoRapid® and regular human insulin correlated well with those in healthy adult subjects and type 1 diabetic adults.

Insulin aspart was rapidly absorbed in both age groups, with similar t_{max} as in adults. However, C_{max} differed between the age groups, stressing the importance of the individual titration of NovoRapid®.

- **Geriatrics:** The relative differences in pharmacokinetic properties between insulin aspart and soluble human insulin in elderly patients (65-83 years, mean age 70 years) with type 2 diabetes were similar to those observed in healthy subjects and in younger patients with diabetes; i.e. the significantly earlier and higher C_{max} is maintained with insulin aspart. As in younger patients with type 2 diabetes, t_{max} of insulin aspart may be slightly delayed in elderly patients with type 2 diabetes, though still significantly earlier than for human insulin.
- **Sex:** There was no significant difference in pharmacokinetics in a trial in type 2 diabetic patients. No significant difference in efficacy, as assessed by A1C, was found between genders in a trial in type 1 diabetic patients.
- **Smoking:** The effect of smoking on the pharmacokinetics and pharmacodynamics of NovoRapid® has not been studied. However, metabolic control was similar in smokers and non-smokers after 6 months treatment with NovoRapid® in the clinical development program
- **Ethnic Origin:** There was no difference in efficacy in terms of blood glucose control as measured by A1C or safety in terms of adverse events between African Americans, Hispanics and Caucasian patients.
- **Hepatic Insufficiency:** Some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. In an open-label, single-dose study of 24 patients with Child-Pugh Scores ranging from 0 (healthy volunteers) to 12 (severe hepatic impairment), no correlation was found between the degree of hepatic failure and any NovoRapid® pharmacokinetic parameter. Careful glucose monitoring and dose adjustments of insulin, including NovoRapid®, may be necessary in patients with hepatic dysfunction. (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic)
- **Renal Insufficiency:** Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. A single subcutaneous dose of

NovoRapid® was administered in a study of 18 patients with creatinine clearance values ranging from normal to <30 mL/min and not requiring hemodialysis. No apparent effect of creatinine clearance values on AUC and C_{max} of NovoRapid® was found. However, only 2 patients with severe renal impairment were studied (<30 mL/min). Careful glucose monitoring and dose adjustments of insulin, including NovoRapid® on AUC and C_{max} of NovoRapid® was found. However, only 2 patients with severe renal impairment were studied (<30 mL/min). Careful glucose monitoring and dose adjustments of insulin, including NovoRapid®, may be necessary in patients with renal dysfunction. (see WARNINGS AND PRECAUTIONS, Renal)

- **Obesity:** The influence of obesity and/or subcutaneous fat thickness on the pharmacokinetics and glucodynamics of NovoRapid® has not been studied. Patients with a body mass index (BMI) up to 40kg/m² were treated with NovoRapid®. No difference was observed in efficacy and safety compared to leaner patients.
- **Others:** The presence of diseases such as Acromegaly, Cushing's syndrome, Hyperthyroidism and Pheochromocytoma can complicate the control of diabetes mellitus.

Detailed Pharmacology

Animal Data

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.

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.

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

There was no significant difference in pharmacokinetics in a trial in type 2 diabetic patients. No significant difference in efficacy, as assessed by A1C was found between genders in a trial in type 1 diabetic patients.

There was no difference in efficacy in terms of blood glucose control as measured by A1C or safety in terms of adverse events between African Americans, Hispanics and Caucasian patients.

11 STORAGE, STABILITY AND DISPOSAL

NovoRapid® (insulin aspart) should be stored between 2-8°C (in a refrigerator) not near a freezing compartment. Do not freeze. Do not expose to excessive heat. In order to protect from

light NovoRapid® should be kept in the outer carton.

In order to protect from light, keep the cap on when NovoRapid® FlexTouch® is not in use.

NovoRapid® vials or Penfill® cartridges: After first opening or carried as a spare: Do not refrigerate. Store below 30°C. Use within 4 weeks.

NovoRapid® FlexTouch®: After first opening or carried as a spare: Store below 30°C. Can be stored in a refrigerator (2°C-8°C). Do not freeze. Use within 4 weeks.

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

NovoRapid® which has been frozen must not be used.

12 SPECIAL HANDLING INSTRUCTIONS

Penfill®/FlexTouch®: Needles and NovoRapid® Penfill®/FlexTouch® should never be shared between patients, even if the needle is changed. The cartridge must not be refilled.

NovoRapid® must not be used if it does not appear water-clear and colourless.

NovoRapid® which has been frozen must not be used.

Penfill®/FlexTouch®: The patient should be advised to discard the needle after each injection.

NovoRapid® may be used in an infusion pump system (CSII). Tubings in which the inner surface materials are made of polyethylene or polyolefin have been evaluated and found compatible with pump use.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

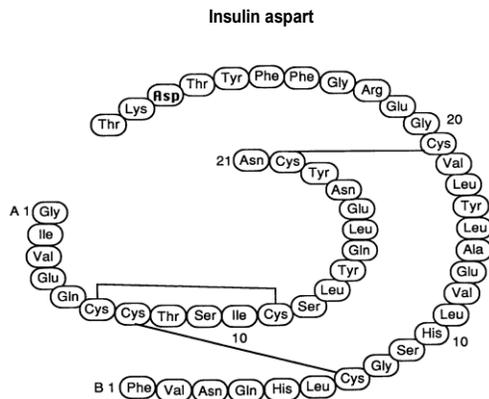
Proper name: Insulin Aspart

Chemical name: B28 asp regular human insulin analogue

Molecular formula and molecular mass: C₂₅₆H₃₈₁N₆₅O₇₉S₆ 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: White, or almost white, amorphous powder

Solubilities:

- in organic solvents like ethanol and methanol: practically insoluble,
- in aqueous solutions with a pH around the isoelectric point of 5.1: practically insoluble
- in aqueous solutions with a pH below 3.5 or above 6.5: solubility is ≥ 25 mg/mL

Absorption:

- hygroscopic; will rapidly absorb significant quantities of moisture in humid environment

1 U (6 nmol = 1 unit) of insulin aspart is equimolar to 1 IU (international unit) of Human Insulin Standard.

Pharmaceutical standard: Professed Standard

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

Postprandial and overall glycemic control: In diabetic patients, NovoRapid® reduced postprandial blood glucose levels and improved the overall glycemic control by significantly reducing A1C as shown in two 6-month multicentre, randomized, parallel, open-label trials. Metabolic control, assessed by A1C was studied in 882 type 1 diabetic patients in one trial and 1065 type 1 diabetic patients in another trial, on a meal-related insulin regimen.

Type 1 Diabetes:

Continuous subcutaneous insulin infusion (CSII) – Pump:

To evaluate the use of NovoRapid® by continuous subcutaneous insulin infusion (CSII) with an external pump, one open-label, randomized, parallel design study for 16 weeks [n=118]⁴

compared NovoRapid® versus Humalog® (insulin lispro) in patients with type 1 diabetes. Glycemic control (as measured by A1C) and rates of hypoglycemia were comparable. Patients with type 2 diabetes were also studied in an open-label, randomized, parallel design trial (24 weeks [n=127]). NovoRapid® by CSII was compared to a basal/bolus regimen of pre-prandial NovoRapid® and basal Novolin®ge NPH injections. Reductions in A1C and rates of hypoglycemia were comparable. In the study (NovoRapid® versus Humalog®), the rate of clogging or blockage events was similar between NovoRapid® and Humalog®.

Pregnancy

The safety and efficacy of an intensified insulin regimen with NovoRapid® was studied in an open-label study in 157 pregnant women with type 1 diabetes. 72% (113) were pregnant prior to entering the study (PBS) and 28% (44) entered the study before conception (PAS). The entry criteria for A1C were different between PBS and PAS ($\leq 8\%$ vs. $\leq 12\%$). PAS patients were withdrawn if A1C was $> 8\%$ at conception, so in this subgroup only women who conceived and had A1C $< 8\%$ had efficacy and safety parameters evaluated. The proportions of patients reaching different A1C targets with NovoRapid® are presented in Table 1.

Table 1: Summary of A1C (%) by Pregnancy status at Screening - ITT Pregnant

| Number of patients | Pregnant at Screening | | | Pregnant after Screening | | | ITT Pregnant | | |
|--------------------------------------|-----------------------|----|------|--------------------------|----|-------|--------------|-----|------|
| | P | N | % | P | N | % | P | N | % |
| Visit P2 (week 12) | | | | | | | | | |
| A _{1c} $\leq 6.0\%$ | 108 | 36 | 33.3 | 31 | 9 | 29.0 | * | * | * |
| A _{1c} $\leq 6.5\%$ | 108 | 70 | 64.8 | 31 | 21 | 67.7 | * | * | * |
| A _{1c} $\leq 7.0\%$ | 108 | 98 | 90.7 | 31 | 26 | 83.9 | * | * | * |
| Visit P3 (week 24) | | | | | | | | | |
| A _{1c} $\leq 6.0\%$ | 102 | 66 | 64.7 | 31 | 13 | 41.9 | 133 | 79 | 59.4 |
| A _{1c} $\leq 6.5\%$ | 102 | 83 | 81.4 | 31 | 27 | 87.1 | 133 | 110 | 82.7 |
| A _{1c} $\leq 7.0\%$ | 102 | 96 | 94.1 | 31 | 30 | 96.8 | 133 | 126 | 94.7 |
| Visit P4 (week 36) | | | | | | | | | |
| A _{1c} $\leq 6.0\%$ | 96 | 53 | 55.2 | 26 | 7 | 26.9 | 122 | 60 | 49.2 |
| A _{1c} $\leq 6.5\%$ | 96 | 77 | 80.2 | 26 | 18 | 69.2 | 122 | 95 | 77.9 |
| A _{1c} $\leq 7.0\%$ | 96 | 90 | 93.8 | 26 | 26 | 100.0 | 122 | 116 | 95.1 |
| Follow-up Visit (6 weeks postpartum) | | | | | | | | | |
| A _{1c} $\leq 6.0\%$ | 104 | 35 | 33.7 | 36 | 8 | 22.2 | 140 | 43 | 30.7 |
| A _{1c} $\leq 6.5\%$ | 104 | 58 | 55.8 | 36 | 20 | 55.6 | 140 | 78 | 55.7 |
| A _{1c} $\leq 7.0\%$ | 104 | 80 | 76.9 | 36 | 26 | 72.2 | 140 | 106 | 75.7 |

P: Number of patients with a A_{1c} measurement at the actual visit

N: Number of patients with a A_{1c} measurement having the given value at the actual visit

%; Proportion of patients with a A_{1c} measurement having the given value at the actual visit

Major and minor hypoglycemia rates for PBS and PAS by trimester are presented in Table 2.

Table 2: All Treatment Emergent Hypoglycemic Episodes During Pregnancy by Treatment, pregnancy status at Screening and trimester - ITT Pregnant

| | IAsp + NPH | | | | |
|--|------------|---|---|---|------|
| | P | N | % | E | Rate |
| | | | | | |

| | | | | | | | |
|--------------------------|--------------------------|-----------------------|-----|---------|---------|------|-------|
| Major | Pregnant at Screening | | | | | | |
| | 1. trimester | 113 | 19 | (16.80) | 34 | 5.2 | |
| | 2. trimester | 113 | 22 | (19.50) | 44 | 1.3 | |
| | 3. trimester | 113 | 9 | (8.00) | 20 | 1 | |
| | Pregnant after Screening | | | | | | |
| | 1. trimester | 44 | 5 | (11.40) | 7 | 0.8 | |
| | 2. trimester | 44 | 5 | (11.40) | 7 | 0.7 | |
| | 3. trimester | 44 | 1 | (2.30) | 1 | 0.2 | |
| | All | | | | | | |
| | 1. trimester | 157 | 24 | (15.30) | 41 | 2.7 | |
| | 2. trimester | 157 | 27 | (17.20) | 51 | 1.2 | |
| | 3. trimester | 157 | 10 | (6.40) | 21 | 0.8 | |
| | Minor | Pregnant at Screening | | | | | |
| | | 1. trimester | 113 | 97 | (85.80) | 907 | 139.4 |
| | | 2. trimester | 113 | 98 | (86.70) | 2992 | 90.9 |
| 3. trimester | | 113 | 85 | (75.20) | 1639 | 83.7 | |
| Pregnant after Screening | | | | | | | |
| 1. trimester | | 44 | 40 | (90.90) | 607 | 69.3 | |
| 2. trimester | | 44 | 33 | (75.00) | 672 | 68.1 | |
| 3. trimester | | 44 | 27 | (61.40) | 380 | 67.4 | |
| All | | | | | | | |
| 1. trimester | | 157 | 137 | (87.30) | 1514 | 98.9 | |
| 2. trimester | | 157 | 131 | (83.40) | 3664 | 85.7 | |
| 3. trimester | | 157 | 112 | (71.30) | 2019 | 80.1 | |
| Symptoms Only | | Pregnant at Screening | | | | | |
| | | 1. trimester | 113 | 32 | (28.30) | 154 | 23.5 |
| | | 2. trimester | 113 | 40 | (35.40) | 407 | 12.4 |
| | 3. trimester | 113 | 34 | (30.10) | 256 | 13.1 | |
| | Pregnant after Screening | | | | | | |
| | 1. trimester | 44 | 24 | (54.50) | 85 | 9.7 | |
| | 2. trimester | 44 | 15 | (34.10) | 118 | 12 | |
| | 3. trimester | 44 | 11 | (25.00) | 35 | 6.2 | |
| | All | | | | | | |
| | 1. trimester | 157 | 56 | (35.70) | 39 | 15.6 | |

| | | | | | | |
|----------------|--------------------------|-----|----|---------|-----|------|
| | 2. trimester | 157 | 55 | (35.00) | 525 | 12.3 |
| | 3. trimester | 157 | 45 | (28.70) | 291 | 11.5 |
| Unclassifiable | Pregnant at Screening | | | | | |
| | 1. trimester | 113 | 4 | (3.50) | 11 | 1.7 |
| | 2. trimester | 113 | 9 | (8.00) | 58 | 1.8 |
| | 3. trimester | 113 | 6 | (5.30) | 34 | 1.7 |
| | Pregnant after Screening | | | | | |
| | 1. trimester | 44 | 4 | (9.10) | 6 | 0.7 |
| | 2. trimester | 44 | 4 | (9.10) | 6 | 0.6 |
| | 3. trimester | 44 | 3 | (6.80) | 27 | 4.8 |

P: Number of patients in the Population

N: Number of patients having Hypoglycemic Episodes

%: Proportion of patients in the Population having Hypoglycemic Episodes

E: Number of Hypoglycemic Episodes

Rate: Number of Hypoglycemic Episodes divided by years of exposure of patients in the Population in the given trimester

The outcome data observed in the human insulin control arm in the NovoRapid® clinical trial are consistent with published trials of human insulin in type 1 diabetes in similar clinical settings.

Geriatrics

A randomised, double-blind, crossover trial compared the pharmacodynamics and pharmacokinetics of a single 0.3 U/kg s.c. dose of insulin apart (IAsp) and single 0.3 U/kg s.c. dose of soluble human insulin (HI) in 19 patients aged 65-83 years (mean age 70 years).

14.2 Study Results

Postprandial and overall glycaemic control:

With NovoRapid®, significantly improved metabolic control was obtained compared to regular human insulin after 6 months treatment, the values being $7.78 \pm 0.03\%$ for NovoRapid® and $7.93 \pm 0.05\%$ ($p < 0.01$) for regular human insulin in one trial and correspondingly $7.88 \pm 0.03\%$ and $8.00 \pm 0.04\%$ ($p < 0.02$) in the other trial. This improvement in glycaemic control with NovoRapid® was accompanied by a significant decrease of postprandial blood glucose levels after each meal, when compared to regular human insulin, without increasing the risk of hypoglycemic events.

Furthermore, NovoRapid® demonstrated a significant decrease in prandial blood glucose increments (defined as the mean difference between the blood glucose value 90 minutes after the meal and the blood glucose value just before the meal, over the 3 meals) when compared to regular human insulin; with values being -1.46 mmol/L in one trial and -1.15 mmol/L in the other; $p < 0.0001$).

Data from an extension to one of these trials ($n=598$) showed that the effect of NovoRapid® on A1C was maintained for 3 years [value being $7.97 \pm 0.11\%$] without increasing the risk of hypoglycemic events.

Type 2 Diabetes

In patients with type 2 diabetes, a randomized, double-blind, multicentre, 2- period, cross-over study showed that 4-hour postprandial glucose excursion in 37 patients (BMI 27.05 ± 4.02 , waist circumference 97.1 ± 11.7 cm) was 20% lower following a single injection of NovoRapid® (injected immediately before a meal test) than regular human insulin (injected 30 minutes before a meal test; $p=0.034$), independent of BMI. The insulin maximum concentration (C_{max}) was significantly higher in patients receiving NovoRapid® ($p=0.023$) and was reached 27 minutes earlier ($p=0.039$), despite the fact that NovoRapid® was injected 30 minutes after human insulin.

In 182 type 2 diabetic patients treated with NovoRapid® in a meal-related regimen for 6 months, the pharmacodynamic properties of NovoRapid® were shown to be not different than regular human insulin with respect to metabolic control as assessed by insulin dose (meal related and NPH).

Geriatrics

IAsp was rapidly absorbed and the t_{max} for IAsp occurred 90 minutes earlier than for HI ($p=0.0089$). C_{max} was on average 132% higher with IAsp than with HI ($p<0.0001$). Also the extent of exposure with IAsp was greater than with HI up to approximately 300 minutes after administration but tended to be lower with IAsp than with HI from 300-600 minutes post dosing. The pharmacodynamic response to a single 0.3 U/kg dose of IAsp and a single 0.3 IU/kg was evaluated during euglycaemic clamp procedures in a cross-over design. Consistent with the pharmacokinetic results, the peak pharmacodynamic activity as determined by maximum value on the glucose infusion rate (GIR) profile was significantly higher ($p=0.0039$) and occurred approximately 83 minutes earlier with IAsp than with HI ($p<0.0001$). The area under the GIR profiles in the interval from 0-120 minutes was on average more than twice as large with IAsp than with HI and this difference was statistically significant ($p<0.0001$). Overall, the pharmacokinetic and pharmacodynamic properties of IAsp are preserved in geriatric patients with type 2 diabetes although a minor delay in peak insulin concentration has been observed when compared with younger patients with type 2 diabetes.

Combination with long-acting basal insulin analog

In an open-label, parallel, randomized trial involving 595 patients with type 1 diabetes, NovoRapid® in combination with insulin detemir significantly improved glycemic control when compared to regular human insulin with NPH insulin treatment. After 18 weeks of treatment, the mean A1C values were $7.88 \pm 0.05\%$ vs $8.11 \pm 0.05\%$ (95% CI; -0.34 to -0.10, $p<0.001$), respectively. In addition, the overall mean postprandial plasma glucose was significantly lower with the combination NovoRapid®/ detemir when compared to regular human insulin/ NPH (7.81 mmol/L vs 7.87 mmol/L, respectively; $p<0.001$) with significant less intra-individual variability in plasma glucose ($p < 0.001$). This improvement of glycemic control was accompanied with a significant decrease in the risk of nocturnal hypoglycemic events (relative risk decreased by 55%; 95% CI 0.35 - 0.58; $p<0.001$) and a significant decrease in body weight ($p<0.001$).

Hypoglycemia

In a 16-week double-blind, randomized, multinational, crossover study with type 1 diabetes patients ($n=156$, A1C $\leq 9.0\%$) the rate of major nocturnal hypoglycemic episodes was 72% lower with NovoRapid® than with regular human insulin {0.067 vs. 0.225 events/month, relative risk 0.28 (95% CI:0.13-0.59); $p=0.001$ }. NPH insulin was given as basal insulin once or twice daily as needed. Furthermore, NovoRapid® significantly reduced the rate of minor

hypoglycemic events when with the rate of minor events was significantly reduced by 7% with NovoRapid® compared to regular human insulin {2.98 vs 3.186 events/months, relative risk 0.93 (95% CI: 0.87-1.00), $p=0.048$ }. While the total rate of major hypoglycemia did not differ significantly between treatments. Reductions in rate of hypoglycemia were achieved with NovoRapid® while maintaining overall glycemic control. The mean A1C remained constant, with values being 7.69% for NovoRapid® and 7.65% for regular human insulin (NS). Significant lower blood glucose values 90 minutes after breakfast ($p=0.0001$) and 90 minutes after dinner ($p=0.023$) were seen with NovoRapid® compared to regular human insulin.

In another study (n=1065), significantly fewer patients (62% less) experienced major nocturnal hypoglycemia with I NovoRapid® than with regular human insulin (1.3 vs 3.4% of patients, respectively; $p<0.005$).

16 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 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. |
| 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 tumours in high dose females. |
| Rat | Sprague-Dawley | 4 Groups 20F | SC | 52 weeks | 200 per drug substance. Insulin aspart, human insulin, control. | Mammary tumour-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 | 4 weeks (+ 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 NovoRapid® (insulin aspart). A series of repeated dose trials in animals (including 52 weeks dosing in rats and dogs) showed that none of the effects observed with NovoRapid® differed from those observed with regular human insulin. In vitro trials showed that the mitogenicity of NovoRapid® does not differ from that observed with regular human insulin. Animal trials on the mutagenic potential of NovoRapid® 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

NovoRapid®

FlexTouch®/Penfill®/vial

Insulin Aspart

Solution for Injection

Read this carefully before you start taking **NovoRapid®** 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 **NovoRapid®**.

Serious Warnings and Precautions

- Hypoglycemia is the most common adverse effect of insulin, including NovoRapid®.
- If hypoglycemia or hypoglycemic 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.
- NovoRapid® should be given immediately before a meal because of the fast onset of action (start of the meal should be not more than 5-10 minutes after injection) (see *How to take NovoRapid®*).
- Never inject your insulin directly into a vein.
- NovoRapid® should not be used if it is not water-clear and colourless.

What is NovoRapid® used for?

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

How does NovoRapid® work?

NovoRapid® is an insulin analogue used to treat diabetes.

NovoRapid® will start to lower your blood sugar 10-20 minutes after you take it, it has a maximum effect between 1 and 3 hours and the effects last for 3-5 hours. Due to this short action NovoRapid® should normally be taken in combination with intermediate-acting or long-acting insulin preparations.

What are the ingredients in NovoRapid® ?

Medicinal ingredients: The active ingredient in NovoRapid® is insulin aspart.

Non-medicinal ingredients: Glycerol; phenol; metacresol; zinc chloride; sodium chloride; disodium phosphate dihydrate; sodium hydroxide; hydrochloric acid and water for injection .

NovoRapid® comes in the following dosage forms:

NovoRapid® is available from Novo Nordisk Canada in the following format:

- NovoRapid® 10 mL vial
- NovoRapid® FlexTouch® 3 mL prefilled pen
- NovoRapid® Penfill® 3 mL cartridge (designed for use with Novo Nordisk Insulin Delivery Devices)

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

Do not use NovoRapid® if:

- You feel a hypoglycemic reaction (low blood sugar) coming on. (see “*What are possible side effects from NovoRapid®?*” for more about hypoglycemia).
- You are allergic (hypersensitive) to insulin aspart, 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 NovoRapid®?*”)
- The Penfill® or Novo Nordisk Insulin Delivery Device containing the cartridge/FlexTouch® is dropped, damaged or crushed; there is a risk of leakage of insulin.
- The protective cap is loose or missing. Each vial has a protective, tamper proof plastic cap. If the cap is not in perfect condition when you get the vial, return the vial to your supplier.
- The insulin has not been stored correctly or if it has been frozen. (see “*How to store NovoRapid®*”)
- The insulin does not appear water-clear and colourless.

Do not refill a NovoRapid® Penfill® cartridge.

NovoRapid® Penfill® cartridges are designed to be used with Novo Nordisk Insulin Delivery Devices, NovoFine®, NovoFine® Plus and NovoTwist® needles as part of **The All In-One System®**.

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

NovoRapid® FlexTouch® is designed to be used with , NovoFine®, NovoFine® Plus and NovoTwist® needles as part of **The All In-One System®**.

As a precautionary measure, you should carry a spare syringe and extra insulin in case the insulin delivery device is lost or damaged.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NovoRapid®. 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 doctor or pharmacist on the availability of NovoRapid® in other countries. If possible, bring enough NovoRapid® 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.

Hypokalemia (low potassium) is a possible side effect with all insulins. You might be more at risk if you are on potassium lowering drugs or losing potassium (e.g. diarrhea).

NovoRapid® has a rapid onset of effect therefore if hypoglycemia occurs, you may experience it earlier after an injection when compared to soluble human insulin.

Other warnings you should know about:

- You may have a very rare serious allergic reaction to NovoRapid® or one of its ingredients (called a generalized allergic reaction). See also the warning in '*Do not use NovoRapid® if*'.
- **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. 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.

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

The following may interact with NovoRapid®:

Some medicines affect the way glucose works in your body and this may influence your insulin dose. Listed below are the most common medicines, which may affect your insulin treatment. 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)
- Sulfonamides (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.

How to take NovoRapid® :

NovoRapid® is for injection under the skin (subcutaneously).

NovoRapid® 10 mL vial is also for continuous infusion in a pump system. NovoRapid® may also be given intravenously by healthcare professionals under close supervision by a doctor.

Always vary the site you inject within the same region, to avoid lumps (see '*What are possible side effects from using NovoRapid®?*'). The best places to give yourself an injection are: the front of your thighs, the front of your waist (abdomen), the upper arm, or the buttocks. 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.

Due to the faster onset of action, NovoRapid® should be given close to a meal (start of the meal should be no more than 5-10 minutes after the injection). When necessary, NovoRapid® can be given soon after a meal, instead of before the meal.

Before using NovoRapid®

- Check the label to make sure you have the right type of insulin.
- Remove the protective cap [vial].
- Always check the Penfill® cartridge, including the plunger. Don't use it if any damage is seen or if there is a gap between the plunger 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 [Penfill® / FlexTouch®].
- Do not share your NovoRapid® FlexTouch® / 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.

If you use only one type of insulin [vial]

- Draw into the syringe the same amount of air as the dose of insulin you are going to inject. Inject the air into the vial.
- Turn the vial and syringe upside down and draw the correct insulin dose into the syringe. Pull the needle out of the vial. Then expel the air from the syringe and check that the dose is correct.

If you have to mix two types of insulin [vial]

- NPH (Neutral Protamine Hagedorn) insulin is the only type of insulin that can be mixed with NovoRapid® and the mixture must be injected immediately under your skin (subcutaneously). . NovoRapid® should be drawn into the syringe before you draw your NPH insulin.
- Just before use, roll the NPH insulin between your hands until the liquid is uniformly white and cloudy.
- Draw into the syringe the same amount of air as the dose of the NPH insulin. Inject the air into the vial containing the NPH insulin and pull out the needle.
- Draw into the syringe the same amount of air as the dose of NovoRapid®. Inject the air into the vial containing NovoRapid®. Turn the vial and syringe upside down and draw up the prescribed dose of NovoRapid®. Expel any air from the syringe and check that the dose is correct.

- Push the needle into the vial of the NPH insulin, turn the vial and syringe upside down and draw out the dose you have been prescribed. Expel any air from the syringe and check the dose. Inject the mixture immediately.
- Always mix NovoRapid® and the NPH insulin in the same order.

How to inject this insulin [vial]

- Pinch your skin between two fingers, push the needle into the skin fold and inject the insulin under the skin.
- Keep the needle under your skin for at least 6 seconds to make sure you have injected all the insulin.

For use in an infusion pump system [vial]:

NovoRapid® should never be mixed with any other insulin when used in a pump.

Follow the instructions and recommendations from your doctor regarding the use of NovoRapid® in a pump. Before using NovoRapid® in a pump system you must receive comprehensive instructions in its use and information about any actions to be taken in case of illness; too high or too low blood sugar; or failure of the pump system.

- Before inserting the needle, use soap and water to wash your hands and the skin around the area where the needle is inserted so as to avoid any infection at the infusion site.
- When you fill a new reservoir, be certain not to leave large air bubbles in either the syringe or the tubing.
- Changing the infusion set (tubing and needle) must be done according to the instructions in the product information supplied with the infusion set.

To get the benefit of insulin infusion, and to detect a possible malfunction of the insulin pump, you should measure your blood sugar level regularly.

What to do in case of pump system failure

You should always have alternative insulin available for injection under the skin in case of pump system failure.

How to inject this insulin [Penfill®]

- Inject the insulin under the skin. Use the injection technique advised by your doctor or Diabetes Nurse Educator and described in your Novo Nordisk Insulin Delivery Device Manual.
- Keep the needle under your skin for at least six 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 discard the needle. Otherwise, the liquid may leak out when the temperature changes.

Overdose:

Causes of a hypoglycemia:

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

If you think you, or a person you are caring for, have taken too much NovoRapid®, 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 NovoRapid®?

These are not all the possible side effects you may have when taking NovoRapid®. If you experience any side effects not listed here, tell your healthcare professional. The most common side effect is low blood sugar (hypoglycemia). See the advice in 'How to take NovoRapid®?'

| 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 | |
| LES COMMON (1 to 10 users in 1000) | | | |
| Signs of allergy: Hives and rash may occur. | | √ | √ |
| Vision problems: disruption of vision when treatment is first started (temporary). | √ | | |
| Changes at the injection site (lipodystrophy): lipoatrophy or lipohypertrophy. | | √ | |
| Swollen joints: When you start taking insulin, water retention may cause swelling around your ankles and other joints. This soon disappears. | √ | | |
| Diabetic retinopathy (eye background changes): If you have diabetic retinopathy and your blood glucose levels improve very fast, the retinopathy may get worse. | | √ | |
| RARE (less than 1 user in 10,000) | | | |
| Painful neuropathy (nerve related pain): If your blood glucose levels improve very fast you may get nerve related pain. This is called acute painful neuropathy and is usually transient. | √ | | |
| 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:

Keep out of the reach and sight of children.

NovoRapid® [vial] that is not being used is to be stored in the refrigerator between 2°C-8°C, in the original package, not in or too near the freezer section or cooling element. Do not freeze.

Always keep the vial in the outer carton when you're not using it in order to protect it from light.

NovoRapid® [Penfill®/FlexTouch®] that is not being used is to be stored in the refrigerator between 2°C to 8°C, away from the cooling element. Do not freeze.

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

NovoRapid® [FlexTouch®]: After first opening or when carried as a spare: You can carry your NovoRapid® FlexTouch® with you and keep it at a temperature below 30°C or in a refrigerator (2°C - 8°C). If refrigerated, keep away from the cooling element. Do not freeze. Use within 4 weeks.

Always keep the Penfill® cartridge in the outer carton when not using it, in order to protect it from light.

Always keep the pen cap on your FlexTouch® when you are not using it, in order to protect it from light.

NovoRapid® should be protected from excessive heat and sunlight.

Do not use NovoRapid® after the expiry date printed on the label and carton.

NovoRapid® 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.

What NovoRapid® looks like and package content

NovoRapid® comes as a water-clear, colourless, aqueous solution in packages of one 10 mL vial per carton.

NovoRapid® Penfill® comes as a water-clear, colourless, aqueous solution in packages of 5 cartridges of 3 mL per carton.

NovoRapid® FlexTouch® comes as a water-clear, colourless, aqueous solution in packages of 1 or 5 prefilled pens of 3 mL per carton.

1 mL contains 100 U (units) of insulin aspart.

1 vial contains 10 mL of insulin aspart equivalent to 1000 U.

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

1 prefilled pen contains 3 mL insulin aspart equivalent to 300 U.

If you want more information about NovoRapid®:

- 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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Novo Nordisk A/S

Manufactured by:

For more information contact:

Novo Nordisk Canada Inc.

Mississauga, Ontario, Canada, L5N 6M1

1 • 800 • 465 • 4334

www.novonordisk.ca

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How to inject this insulin

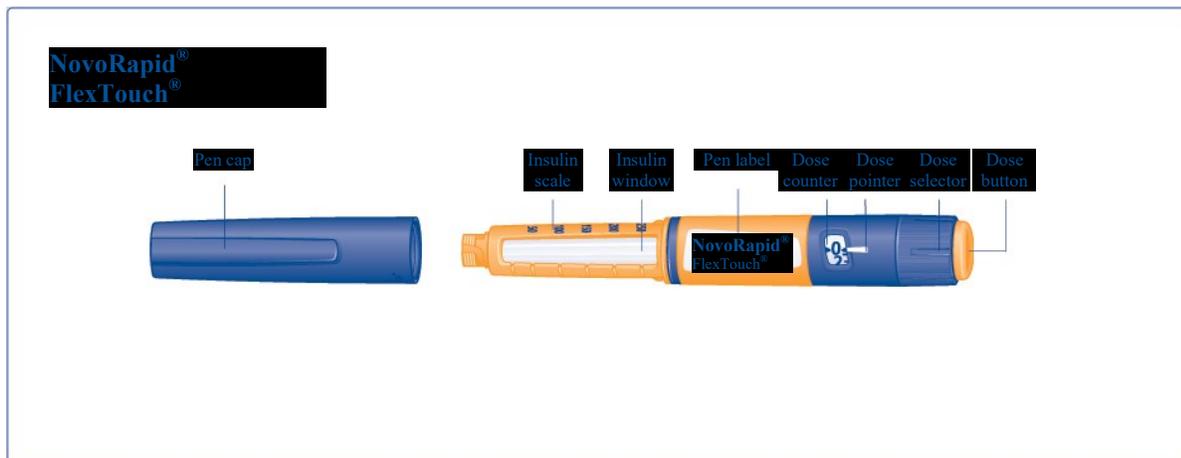
Please read these instructions carefully before using your FlexTouch® pre-filled pen. If you do not follow the instructions carefully, you may get too little or too much insulin, which can lead to too high or too low blood sugar level.

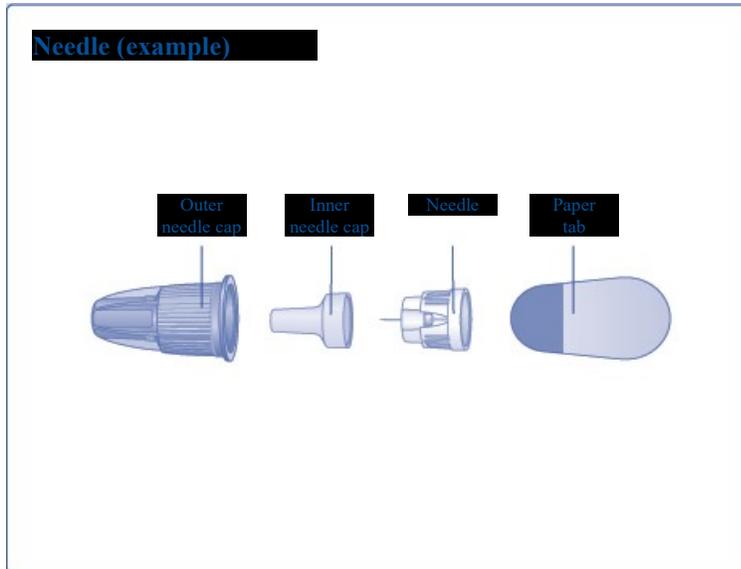
Do not use the pen without proper training from your doctor or nurse. Start by checking your pen to **make sure that it contains NovoRapid® 100 U/ml**, then look at the illustrations to the right to get to know the different parts of your pen and needle.

If you are blind or have poor eyesight and cannot read the dose counter on the pen, do not use this pen without help. Get help from a person with good eyesight who is trained to use the FlexTouch® pre-filled pen.

Your NovoRapid® FlexTouch® pen is a prefilled insulin pen. NovoRapid® FlexTouch® contains 300 units of insulin and delivers doses from 1-80 units, in increments of 1 unit. NovoRapid® FlexTouch® is designed to be used with **NovoFine®, NovoFine® Plus and/or NovoTwist®** single-use disposable needles up to a length of 8 mm. Do not share your NovoRapid® FlexTouch® with another person, even if the needle is changed. You may give another person an infection, or get an infection from them.

NovoRapid® FlexTouch®

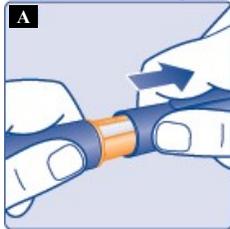




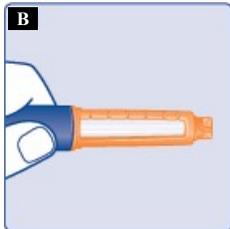
Preparing your NovoRapid® FlexTouch® pen

Check the name and coloured label on your NovoRapid® FlexTouch® pen to make sure that it contains the type of insulin you need. This is especially important if you take more than one type of insulin. If you take a wrong type of insulin, your blood sugar level may get too high or too low.

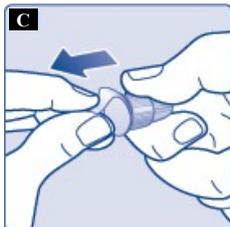
A Pull off the pen cap.



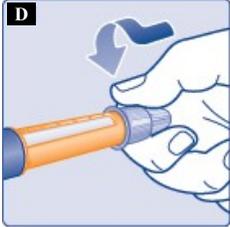
B Check that the insulin in your pen is clear and colourless. Look through the insulin window. If the insulin looks cloudy, do not use the pen.



C Take a new disposable needle, and tear off the paper tab.



D Screw the needle straight onto the pen. Make sure the needle is on tight.



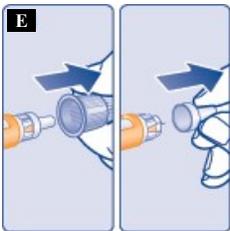
E Pull off the outer needle cap and save it.

You will need it after the injection to correctly remove the needle from the pen.

Pull off the inner needle cap and throw it away.

If you try to put it back on, you may accidentally stick yourself with the needle.

A drop of insulin may appear at the needle tip. This is normal.



■ **Always use a new needle for each injection.** This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing. Do not reuse or share needles with another person including family members.

■ **Never use a bent or damaged needle.**

Checking the insulin flow

Make sure that you receive your full dose by always checking the insulin flow before you select and inject your dose.

F Turn the dose selector to select 2 units.



G Hold the pen with the needle pointing up.

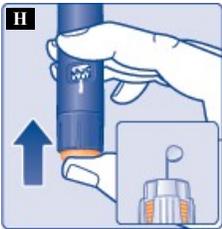
Tap the top of the pen a few times to let any air bubbles rise to the top.



H Press the dose button with your thumb until the dose counter returns to zero. The 0 must line up with the dose pointer. A drop of insulin will appear at the needle tip.

If no drop appears, repeat steps **F** to **H** up to 6 times. If no drop appears after these new attempts, change the needle and repeat steps **F** to **H** once more.

Do not use the pen if a drop of insulin still does not appear.



■ **Always make sure that a drop appears** at the needle tip before you inject. This makes sure that the insulin flows. If no drop appears, you will **not** inject any insulin, even though the dose counter may move. This may indicate a blocked or damaged needle.

■ **Always check the flow before you inject.** If you do not check the flow, you may get too little insulin or no insulin at all. This may lead to too high blood sugar level.

Selecting your dose

Use the dose selector on your NovoRapid® FlexTouch® pen to select your dose. You can select up to 80 units per dose.

I Select the dose you need. You can turn the dose selector forwards or backwards.

Stop when the right number of units lines up with the dose pointer.

The dose selector clicks differently when turned forwards, backwards or past the number of units left.

When the pen contains less than 80 units, the dose counter display stops at the number of units left.



▲ Always use the dose counter and the dose pointer to see how many units you have selected before injecting the insulin.

Do not count the pen clicks. If you select and inject the wrong dose, your blood sugar level may get too high or too low.

Do not use the insulin scale, it only shows approximately how much insulin is left in your pen.

How much insulin is left?

The **insulin scale** shows you **approximately** how much insulin is left in your pen.



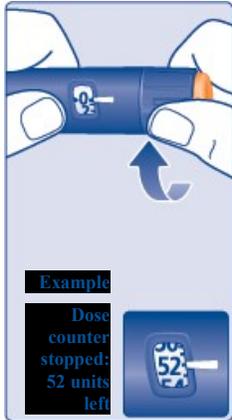
To see precisely how much insulin is left, use the dose counter:

Turn the dose selector until the **dose counter stops**. If it shows 80, **at least 80** units are left in your pen.

If it shows **less than 80**, the number shown is the number of units left in your pen.

Turn the dose selector back until the dose counter shows 0.

If you need more insulin than the units left in your pen, you can split your dose between two pens.



▲ Be very careful to calculate correctly if splitting your dose.

If in doubt, take the full dose with a new pen. If you split the dose wrong, you will inject too little or too much insulin, which can lead to too high or too low blood sugar level.

Injecting your dose

Make sure that you receive your full dose by using the right injection technique.

J Insert the needle into your skin as your doctor or Diabetes Nurse Educator has shown you. Make sure you can see the dose counter. Do not touch the dose counter with your fingers. This could interrupt the injection.

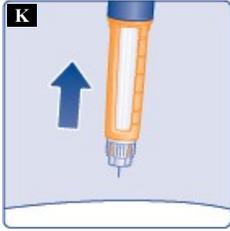
Press the dose button until the dose counter returns to 0. The figure 0 must line up with the dose pointer. You may then hear or feel a click.

After the dose counter has returned to 0, leave the needle under the skin for **at least 6 seconds** to make sure that you get your full dose.



K Remove the needle from the skin.

After that, you may see a drop of insulin at the needle tip. This is normal and has no effect on the dose you just received.

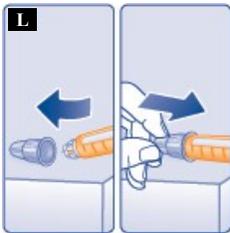


Always dispose of the needle after each injection. This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing. If the needle is blocked, you will **not** inject any insulin.

L Lead the needle tip into the outer needle cap on a flat surface. Do not touch the needle or the cap.

Once the needle is covered, carefully push the outer needle cap completely on and then unscrew the needle. Dispose of it carefully, and put the pen cap back on after every use.

When the pen is empty, throw it away without a needle on as instructed by your doctor, Diabetes Nurse Educator or local authorities.



▲ Always watch the dose counter to know how many units you inject.

The dose counter will show the exact number of units. Do not count the pen clicks. Hold the dose button down until the dose counter returns to 0 after the injection. If the dose counter stops before it returns to 0, the full dose has not been delivered, which may result in too high blood sugar level.

▲ Never try to put the inner needle cap back on the needle. You may stick yourself with the needle.

▲ Always remove the needle after each injection and store your pen without the needle attached. This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.

Caring for your pen

Treat your pen with care. Rough handling or misuse may cause inaccurate dosing, which can lead to too high or too low blood sugar level.

- **Do not leave the pen in a car** or other place where it can get too hot or too cold.
- **Do not expose your pen to dust, dirt or liquid.**
- **Do not wash, soak or lubricate your pen.** If necessary, clean it with mild detergent on a moistened cloth.

- **Do not drop your pen** or knock it against hard surfaces.
If you drop it or suspect a problem, attach a new needle and check the insulin flow before you inject.
- **Do not try to refill your pen.** Once empty, it must be disposed of.
- **Do not try to repair your pen** or pull it apart.

Important information

- **Always keep your pen with you.**
- **Always carry an extra pen and new needles** with you, in case of loss or damage.
- Always keep your pen and needles **out of sight and reach of others**, especially children.
- **Never share** your pen or your needles with other people. It might lead to cross-infection.
- **Never share** your pen with other people. Your medicine might be harmful to their health.

Caregivers must **be very careful when handling used needles** to reduce the risk of needle injury and cross-infection.