

PRODUCT MONOGRAPH

Schedule D

NovoRapid®

Insulin Aspart

Solution for Injection

100 Units/mL

Professed Standard

Antidiabetic Agent

| | |
|---|---------------------------------------|
| Novo Nordisk Canada Inc. 300-2680 Skymark Avenue Mississauga, Ontario L4W 5L6 Canada | Date of Approval: 19-February 2009 |
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NovoRapid®

Insulin Aspart

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|-------------------------|--------------------------------------|--|
| Subcutaneous Injection | solution for injection, 100 Units/mL | disodium phosphate dihydrate, glycerol, hydrochloric acid, metacresol, phenol, sodium chloride, sodium hydroxide 2N, zinc chloride solution, water for injection <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i> |

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.

INDICATIONS AND CLINICAL USE

NovoRapid® (insulin aspart) is indicated for 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.

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 ACTION AND CLINICAL PHARMACOLOGY.

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 ACTION AND CLINICAL PHARMACOLOGY.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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.

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 activity³. **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.

Hypokalemia is among the potential clinical adverse effect associated with the use of all insulins. This potential clinical adverse effect may be relevant in patients who are on potassium lowering drugs⁴.

Stress or illness may increase insulin requirements. In these instances, patients should contact their physician and carefully control their blood glucose³.

Any change of insulin dose should be made cautiously and only under medical supervision. Transferring a patient to a new type or brand of insulin should be done under strict medical supervision. Changes in insulin strength, brand type (e.g., regular, NPH, analogue), species (animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage. Patients taking **NovoRapid®** may need a change in dosage from that used with their previous insulin.

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

Endocrine and Metabolism

Glucose monitoring is recommended for all patients with diabetes.

Hypoglycemia

In certain cases (long duration of diabetes, diabetic nerve disease, intensified diabetes control, or use of medications such as beta blocking agents), the nature and intensity of early warning symptoms of hypoglycemia may change or be less pronounced⁵.

Hypoglycemia is the most frequently occurring undesirable effect of insulin therapy. 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.^{23, 24}

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

Changes in insulin therapy or changes in life style (i.e. diet, exercise/physical activity) may require a change in dosage.

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).

Hyperglycemia

Inadequate dosing or discontinuation of insulin treatment, especially in type 1 diabetes, may lead to hyperglycemia and diabetic ketoacidosis. Severe sustained hyperglycemia may result in diabetic coma and death.

Hepatic/Biliary/Pancreas

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).³² . 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 subjects 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 subjects with moderate and severe hepatic impairment. AUC, C_{\max} and CL/F were similar in subjects with reduced hepatic function compared with subjects with normal hepatic function.

Immune

Insulin antibodies may develop during treatment with insulin. 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 subjects 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 subjects 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 Function/Reproduction and Special Populations, Pregnant Women, ADVERSE REACTIONS, Clinical Trial Adverse Drug

Reactions, Pregnancy clinical trials; and Part II, SCIENTIFIC INFORMATION, CLINICAL TRIALS, type 1 Diabetes.

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}) 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**[®] ³². 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 subjects with moderate and severe renal impairment. Subject with renal failure necessitating dialysis treatment were not investigated.

Sexual Function/Reproduction

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.

Pregnancy:

Congenital anomalies are three to four 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%) subjects treated with NovoRapid[®]. Cardiac anomalies were reported (n=7) mainly septal defects (n=4). Additional reports in patients treated with NovoRapid[®] were one each of central nervous system anomaly, ankyloglossia and feta 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, Immune and Special Populations, Pregnant Women; ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, Pregnancy clinical

trials; and Part II, SCIENTIFIC INFORMATION, CLINICAL TRIALS, type 1 Diabetes.

Skin

Local allergic reaction

As with other insulins, patients may experience redness, swelling or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks. They may occur if the injection is not properly made, or if the patient is allergic to the insulin or any excipients⁶. Few local injection site reactions were observed with **NovoRapid**[®] in the clinical development program and there was no difference in frequency when compared to regular human insulin.

Special Populations

Pregnant Women

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 third (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[®].

Nursing Women:

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

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.

Geriatrics (> 65 years of age):

A 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 subjects with diabetes. However, careful glucose monitoring and individual dose adjustments of insulin, including insulin aspart, may be necessary in elderly patients. Please see ACTION AND 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.

Gender - 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.

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.¹³

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.

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

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 glycosylated hemoglobin is recommended for the monitoring of long-term glycemic control. If 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

Clinical Trial Adverse Drug Reactions

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

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 (>1/1,000, <1/100) and rare (>1/10,000, <1/1,000). Isolated spontaneous cases are presented as very rare defined as (<1/10,000).

Immune system disorders:

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

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

Uncommon (>1/1,000, <1/100): Diabetic retinopathy

Long-term improved glycaemic 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 (>1/1,000, <1/100): Lipodystrophy

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

Uncommon (>1/1,000, <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 (>1/1,000, <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 subjects 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 subjects 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, Immune, and Sexual Functions/reproduction and Special populations; Pregnant Women; and Part II, SCIENTIFIC INFORMATION, CLINICAL TRIALS, type 1 Diabetes.

Less Common Clinical Trial Adverse Drug Reactions (<1%):

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.

Post-Market Adverse Drug Reactions:

Adverse Drug Event Overview for a Post-Marketing CSII Trial

A 4 month post-marketing study in 511 subjects 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 seven 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.

DRUG INTERACTIONS

Overview

Concomitant use of other drugs may influence insulin requirements.

Mixing of insulins

If **NovoRapid**[®] (insulin aspart) is mixed with an intermediate-acting or long-acting insulin, **NovoRapid**[®] should be drawn into the syringe first. The injection should be made immediately after mixing. 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.

The effects 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.

Drug-Drug Interactions

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

Other drugs may increase insulin requirements: oral contraceptives, thiazides, glucocorticosteroids, thyroid hormones, sympathomimetics and danazol. Beta blocking agents may mask the symptoms of hypoglycemia. Alcohol may intensify and prolong the hypoglycemic effect of insulin.

Drug-Food Interactions

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

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory 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 insulin⁸.

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

DOSAGE AND ADMINISTRATION

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.

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 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.

Administration

NovoRapid[®] (insulin aspart) is administered subcutaneously in the abdominal wall, the thigh, buttocks or the upper arm. Injection sites should be rotated within the same region.

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 clear and colourless. **NovoRapid**[®] should not be used after its expiration date.

If **NovoRapid**[®] is mixed with an intermediate-acting or long-acting insulin, **NovoRapid**[®] should be drawn into the syringe first. The injection should be made immediately after mixing. **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.⁸

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.

HYPOGLYCEMIA AND OVERDOSAGE

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

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

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The primary activity of **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 post prandial insulin release than regular human insulin used as replacement therapy. This effect leads to reduced post prandial variability in blood glucose concentration.

In patients with diabetes mellitus, postprandial blood glucose levels are identified as a predictor of A1C levels.^{15, 16, 27} Furthermore, postprandial glucose control is an independent risk factor for

morbidity and mortality in diabetics.^{16,18} This has been demonstrated with regard to overall mortality and cardiovascular disease and death.^{19,20} 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 recommended⁸.

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 is 3 to 5 hours.

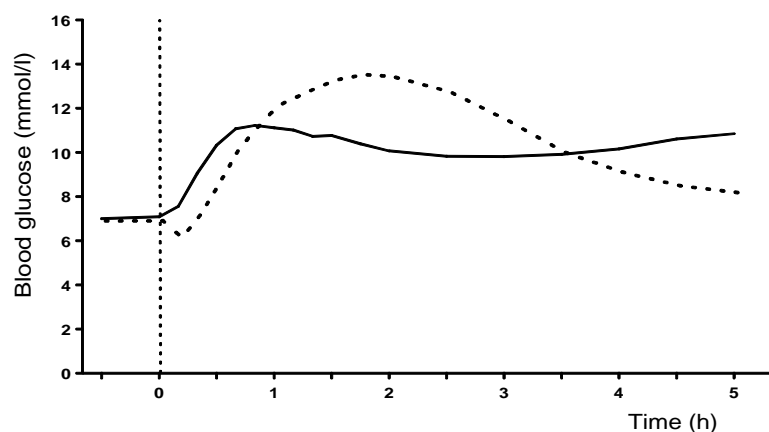


Fig. 1 Mean blood glucose levels following a single pre-meal subcutaneous dose (0.15U/kg) of NovoRapid[®] injected immediately before a meal (solid line) or regular human insulin administered 30 minutes before a meal (hatched line) in 22 patients with type 1 diabetes.

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 subjects 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.

Pharmacokinetics

In NovoRapid® substitution of the amino acid profile 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 to 50 minutes for **NovoRapid®** versus 80 to 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.¹

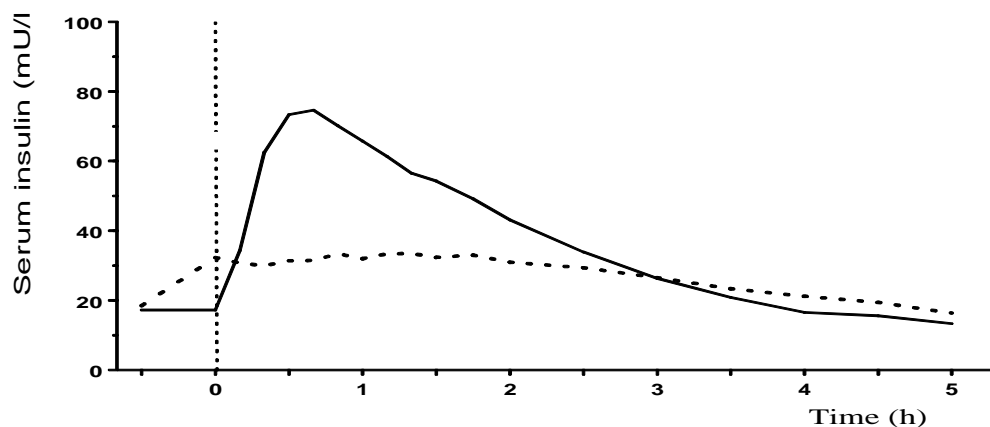


Fig 2 Mean serum insulin concentration following a single pre-meal subcutaneous dose (0.15U/kg body weight) of **NovoRapid**[®] injected immediately before a meal (solid line) or regular human insulin administered subcutaneously 30 minutes before a meal (hatched line) in 22 patients with type 1 diabetes.

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 subjects (Figure 3 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 to 5 hours compared to 5 to 8 hours for regular human insulin. In this trial, subjects were clamped from the evening before the trial product administration in order to obtain a blood glucose concentration of 5 to 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 to 7 mmol/l or 72 to 126mg/dl) were significantly lower with **NovoRapid**[®] than with regular human insulin².

The extent of absorption (AUC) and $t_{max(ins)}$ 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;⁹ none of the insulin metabolites formed following cleavage are active.^{10, 11, 12}

Excretion:

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 subjects (65-83 years, mean age 70 years) with type 2 diabetes were similar to those observed in healthy subjects and in younger subjects with diabetes; i.e. the significantly earlier and higher C_{max} is maintained with insulin aspart. As in younger subjects with type 2 diabetes, t_{max} of insulin aspart may be slightly delayed in elderly subjects with type 2 diabetes, though still significantly earlier than for human insulin.

Gender:

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.

Race:

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.

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.

STORAGE AND STABILITY

Temperature:

NovoRapid[®] (insulin aspart) should be stored between 2 and 10°C (in a refrigerator) not near a freezing compartment. Do not freeze. Do not expose to excessive heat. Penfill[®] cartridges or vials in use or carried as a spare may be kept at ambient temperature (not above 30°C) for up to 4 weeks.

Light:

In order to protect from light, keep the cap on when **NovoRapid**[®] Penfill[®] in a Novo Nordisk Insulin Delivery Device is not in use. Keep out of sunlight.

Others:

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

NovoRapid[®] (insulin aspart) is available in 10 ml vials (in cartons of 1 vial) and in 3 ml Penfill[®] cartridges (in cartons of 5 cartridges). Each presentation is in a strength of 100 Units of insulin aspart per ml.

The vials are made of type 1 glass and are closed with a bromobutyl/polyisoprene rubber disc and a protective tamper-proof plastic cap.

NovoRapid[®] Penfill[®] cartridges are designed for use with Novo Nordisk Insulin Delivery Devices and **NovoFine**[®] needles as part of the All-In-One-System[®].

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

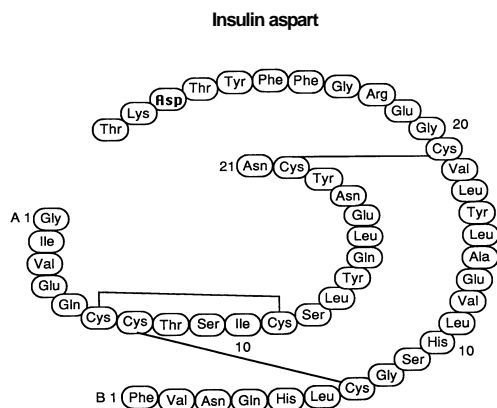
Drug Substance

Proper name: Insulin Aspart

Chemical name: B28 asp regular human insulin analogue

Molecular formula and molecular mass: $C_{256}H_{381}N_{65}O_{79}S_6$ and 5825.8 g/mole
 Insulin aspart is an analogue of human insulin, in which the amino acid proline in position B28 has been replaced by aspartic acid

Structural formula of insulin aspart:



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.

Product Characteristics

The manufacture of the drug substance consists of the following three major steps: fermentation,

recovery, and purification. In the recovery phase, the fermentation broth undergoes an alkaline treatment and the yeast cells are removed by centrifugation

CLINICAL TRIALS

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.^{21,22} 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 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 glycemic 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; $p < 0.0001$).^{21,22}

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.²³

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.³³ Seventy two percent (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 subjects 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 the following table.

Summary of A1c (%) by Pregnancy status at Screening - ITT_{Pregnant}

| | Pregnant at Screening | | | Pregnant after Screening | | | ITT Pregnant | | |
|---------------------------------------|-----------------------|----|------|--------------------------|----|-------|--------------|-----|------|
| | P | N | % | P | N | % | P | N | % |
| Number of subjects | 113 | | | 44 | | | 157 | | |
| 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 post partum) | | | | | | | | | |
| 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 subjects with a A_{1c} measurement at the actual visit

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

%; Proportion of subjects 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 the following table.

All Treatment Emergent Hypoglycaemic Episodes During Pregnancy by Treatment, pregnancy status at Screening and trimester - ITT Pregnant

| | | P | N | IAsp + NPH (%) | E | Rate | |
|--------------------------|--------------------------|-----------------------|-----|-------------------|--------|-------|------|
| Major | Pregnant at Screening | | | | | | |
| | 1. trimester | 113 | 19 | (16.8) | 34 | 5.2 | |
| | 2. trimester | 113 | 22 | (19.5) | 44 | 1.3 | |
| | 3. trimester | 113 | 9 | (8.0) | 20 | 1.0 | |
| | Pregnant after Screening | | | | | | |
| | 1. trimester | 44 | 5 | (11.4) | 7 | 0.8 | |
| | 2. trimester | 44 | 5 | (11.4) | 7 | 0.7 | |
| | 3. trimester | 44 | 1 | (2.3) | 1 | 0.2 | |
| | All | | | | | | |
| | 1. trimester | 157 | 24 | (15.3) | 41 | 2.7 | |
| | 2. trimester | 157 | 27 | (17.2) | 51 | 1.2 | |
| | 3. trimester | 157 | 10 | (6.4) | 21 | 0.8 | |
| Minor | Pregnant at Screening | | | | | | |
| | 1. trimester | 113 | 97 | (85.8) | 907 | 138.4 | |
| | 2. trimester | 113 | 98 | (86.7) | 2992 | 90.9 | |
| | 3. trimester | 113 | 85 | (75.2) | 1639 | 83.7 | |
| | Pregnant after Screening | | | | | | |
| | 1. trimester | 44 | 40 | (90.9) | 607 | 69.3 | |
| | 2. trimester | 44 | 33 | (75.0) | 672 | 68.1 | |
| | 3. trimester | 44 | 27 | (61.4) | 380 | 67.4 | |
| | All | | | | | | |
| | 1. trimester | 157 | 137 | (87.3) | 1514 | 98.9 | |
| | 2. trimester | 157 | 131 | (83.4) | 3664 | 85.7 | |
| | 3. trimester | 157 | 112 | (71.3) | 2019 | 80.1 | |
| | Symptoms only | Pregnant at Screening | | | | | |
| | | 1. trimester | 113 | 32 | (28.3) | 154 | 23.5 |
| | | 2. trimester | 113 | 40 | (35.4) | 407 | 12.4 |
| 3. trimester | | 113 | 34 | (30.1) | 256 | 13.1 | |
| Pregnant after Screening | | | | | | | |
| 1. trimester | | 44 | 24 | (54.5) | 85 | 9.7 | |
| 2. trimester | | 44 | 15 | (34.1) | 118 | 12.0 | |
| 3. trimester | | 44 | 11 | (25.0) | 35 | 6.2 | |
| All | | | | | | | |
| 1. trimester | | 157 | 56 | (35.7) | 239 | 15.6 | |
| 2. trimester | | 157 | 55 | (35.0) | 525 | 12.3 | |
| 3. trimester | | 157 | 45 | (28.7) | 291 | 11.5 | |
| Unclassifiable | Pregnant at Screening | | | | | | |
| | 1. trimester | 113 | 4 | (3.5) | 11 | 1.7 | |
| | 2. trimester | 113 | 9 | (8.0) | 58 | 1.8 | |
| | 3. trimester | 113 | 6 | (5.3) | 34 | 1.7 | |
| | Pregnant after Screening | | | | | | |
| | 1. trimester | 44 | 4 | (9.1) | 6 | 0.7 | |
| | 2. trimester | 44 | 4 | (9.1) | 6 | 0.6 | |
| | 3. trimester | 44 | 3 | (6.8) | 27 | 4.8 | |

P: Number of subjects in the Population

N: Number of subjects having Hypoglycaemic Episodes

?: Proportion of subjects in the Population having Hypoglycaemic Episodes

E: Number of Hypoglycaemic Episodes.

Rate: Number of Hypoglycaemic Episodes divided by years of exposure of subjects 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.

Type 2 Diabetes:

In patients with type 2 diabetes, a randomized, double-blind, multicentre, two 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.¹³

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: A randomised, double-blind, crossover trial compared the pharmacodynamics and pharmacokinetics of a single 0.3 U/kg s.c. dose of insulin aspart (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). 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 to 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 min earlier with IAsp than with HI (p<0.0001). The area under the GIR profiles in the interval from 0 to 120 min 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 subjects with type 2 diabetes although a minor delay in peak insulin concentration has been observed when compared with younger subjects 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 ($p < 0.001$).¹⁴

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 hypoglycaemia with 1 **NovoRapid**[®] than with regular human insulin (1.3 vs 3.4% of patients, respectively; $p < 0.005$).²¹

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 hypoglycaemic 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 |

| Test | Insulin Aspart/ Human Insulin(HI) | Results |
|--|--|---|
| 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.

TOXICOLOGY

Acute Toxicity:

Table [1]: Results of Acute Toxicity Studies with Insulin aspart

| Species, Strain, Route | (M+F) Animals per group | Doses (U/kg) | Results |
|------------------------|-------------------------|--------------------------|--|
| Mouse NMRI. SC | 5 + 5 | 0, 62.5, 250, 1000, 4000 | Highest non-lethal dose: 4000U/kg in males and 250U/kg in females. |

| Species, Strain, Route | (M+F) Animals per group | Doses (U/kg) | Results |
|------------------------|-------------------------|------------------------------------|--|
| Mouse, CD1, SC | 5 + 5 | 0, 62.5, 250, 1000, 4000 | Highest non-lethal dose: 4000U/kg |
| Mouse, NMRI, IV | 5 + 5 | 0, 62.5, 250, 1000, 4000 | Highest non-lethal dose: 4000U/kg in males and 1000 u/kg in females |
| Rat, S.D. SC | 5 + 5 | 0, 62.5, 250, 1000, 4000 | Highest non-lethal dose: 4000U/kg |
| Rat, S.D. SC | 5 + 5 | 0, 62.5, 250, 1000, 2000. | Highest non-lethal dose: 2000Ukg |
| Rat, S.D. SC | 5 + 5 | 0, 62.5, 250, 1000, 4000 | Highest non-lethal dose: 4000U/kg |
| Rat, S.D. IV | 5 + 5 | 0, 62.5, 250, 1000, 4000 | Highest non-lethal dose: 4000 U/kg |
| Dog, Beagle, SC. | 1 + 1 | 4, 8, 16, 32, 64 64 Old process | Highest non-lethal dose: 64U/kg Apart from hypoglycemia no treatment-related signs or changes |

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

Long-term Toxicity:

Table [2]: 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 | Hypoglycemia, increased food and water consumption and weight gain. Excess of mammary tumours in high dose females. |

| Species | Strain | Number of groups and size | Dosing Method | Duration (Weeks) | Dose level (U/kg/day) | Results |
|---------|----------------|---|---------------|--|---|---|
| | | | | | weeks 10 and 50 od for 27-52 weeks. Controls. | |
| 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 | 4weeks (+ 4 week recovery in groups 1 & 4) | 0, 0.25, 0.5 , 1.0 bid | Hypoglycaemia. No unexpected observations. |
| Dog | Beagle | 3 Groups 4M, 4F | SC | 13 weeks | 0,1, 4 | Hypoglycaemia. 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 | Hypoglycaemia. 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.

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PART III: CONSUMER INFORMATION

Important: Please Read

NovoRapid[®]
[Penfill[®]]
Insulin Aspart
Solution for Injection

10 mL / 3 mL

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

Read all of this leaflet carefully before you start using your insulin. Keep this leaflet. You may need to read it again.

If you have any further questions, ask your doctor, Diabetes Nurse Educator or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, diabetes nurse or your pharmacist.

If you have trouble reading this, ask a family member or a friend for help.

ABOUT THIS MEDICATION

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

What is NovoRapid[®]
[Penfill[®]]

NovoRapid[®] (insulin aspart) is an insulin analogue used to treat diabetes. It comes in a 10 mL vial that you use with a syringe and 3 mL cartridge called Penfill[®], which fits into a Novo Nordisk Insulin Delivery device.

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

NovoRapid[®] (insulin aspart) is indicated for:

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

When NovoRapid[®] should not be used

Do not use NovoRapid[®]:

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

What the medicinal ingredient is

The active ingredient in NovoRapid® is insulin aspart made by recombinant DNA technology.

What the important nonmedicinal ingredients are

Glycerol; phenol; metacresol; zinc chloride; sodium chloride; disodium phosphate dihydrate; sodium hydroxide; hydrochloric acid and water for injection.

What dosage forms NovoRapid® comes in

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

NovoRapid® 10 mL vial

NovoRapid® Penfill® 3 mL cartridge

(designed for use with Novo Nordisk Insulin Delivery Devices)

NovoRapid® [Penfill®] is designed for use with NovoFine® 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® needles.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **NovoRapid® should not be used if it is not water-clear and colourless.**

Before you use NovoRapid® [Penfill®]

Before you use NovoRapid® [vial / Penfill®] talk to your doctor or pharmacist:

- ▶ **If you have trouble** with your kidneys or liver, your doctor may decide to alter your insulin dose.
- ▶ **If you drink alcohol (including wine and beer):** watch for signs of a hypo and never drink alcohol on an empty stomach.
- ▶ **If you exercise more than usual** or if you want to change your usual diet.
- ▶ **If you are ill:** continue taking your insulin. Your need for insulin may change.
- ▶ **If you have an infection, fever or have had an operation** you may need more insulin than usual.
- ▶ **If you suffer from diarrhea, vomiting or eat less than usual** you may need less insulin than usual.
- ▶ **If you 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.
- ▶ **If you are pregnant, or planning a pregnancy or are breastfeeding** please contact your doctor for advice.
- ▶ **If you drive or use tools or machines:** watch for signs of a hypo. Your ability to concentrate or to react will be less during a hypo. Please keep this in mind in all situations where you might put

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

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

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

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.

INTERACTIONS WITH THIS MEDICATION

When you use other medicines

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

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

PROPER USE OF THIS MEDICATION

How to use NovoRapid® [Penfill®]

Talk about your insulin needs with your doctor and Diabetes Nurse Educator. 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.

It is recommended that you measure your blood glucose regularly.

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 rubber stopper (plunger). Don't use it if any damage is seen or if there is a gap between the rubber stopper and the white barcode label. Take it

back to your supplier or call Novo Nordisk Canada at 1 800 465-4334 for assistance. See your Novo Nordisk Insulin Delivery Device manual for further instructions.

- ▶ **Disinfect** the rubber membrane with an alcohol swab [vial / Penfill[®]].
- ▶ Always use a new needle for each injection to prevent contamination [Penfill[®]].

Do not use NovoRapid[®]:

- ▶ **If 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.
- ▶ **If the Penfill[®] cartridge or Novo Nordisk Insulin Delivery Device containing the cartridge is dropped, damaged or crushed;** there is a risk of leakage of insulin.
- ▶ **If the insulin has not been stored correctly** or if it has been frozen (see '*How to Store NovoRapid[®]*').
- ▶ **If the insulin does not appear clear and colourless.**

How to use this insulin

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 '*Possible side effects*'). The best places to give yourself an injection are: your buttocks; the front of your thighs; the front of your waist (abdomen); or the upper arm. Your insulin will work more quickly if you inject around the waist.

NovoRapid[®] Penfill[®] is designed to be used with Novo Nordisk Insulin Delivery Devices and NovoFine[®] needles as part of **The All-In-One System[®]**.

If you are treated with NovoRapid[®] Penfill[®] and another insulin in Penfill[®] cartridge, you must use two insulin delivery devices, one for each type of insulin.

Do not refill NovoRapid[®] Penfill[®].

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

You should always measure your blood glucose regularly.

How to inject this insulin

If you use only one type of insulin [vial]:

1. 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.
2. 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]

1. Just before use, roll the long-acting (cloudy) insulin between your hands until the liquid is uniformly white and cloudy.

2. Draw into the syringe the same amount of air as the dose of long-acting insulin. Inject the air into the vial containing long-acting insulin and pull out the needle.
3. 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.
4. Push the needle into the vial of long-acting 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.
5. Always mix NovoRapid[®] and long-acting 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 insulin delivery device manual.
- ▶ **Keep the needle under your skin** for at least 6 seconds to make sure that the full dose has been delivered.
- ▶ **After each injection** be sure to discard the needle. Otherwise, the liquid may leak out when the temperature changes.

Overdose

Causes of a hypo:

- You get a hypo if your blood sugar gets too low. This might happen:
- If you take too much insulin.
- If you eat too little or miss a meal.

- If you exercise more than usual.

If your blood sugar gets too high:

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

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

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

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

Causes of hyperglycemia:

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

**SIDE EFFECTS AND
WHAT TO DO ABOUT THEM**

*What to do
in an emergency*

If you get a hypo (hypoglycemia)

A hypo means your blood sugar level is too low.

The warning signs of a hypo may come on suddenly and can include: cold sweat; cool pale skin; headache; rapid heart beat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; and difficulty concentrating.

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

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

If you feel a hypo coming on: take a high sugar snack and then measure your blood sugar.

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

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

- ▶ **If severe hypoglycemia is not treated,** it can cause brain damage (temporary or permanent) and even death.

- ▶ **If you have a hypo that makes you pass out**, or if you get a lot of hypos, talk to your doctor. The amount or timing of your insulin dose, the amount of food you eat or the amount of exercise you do, may need to be adjusted.

Using glucagon

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

Possible side effects

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

Less commonly reported side effects

(less than 1 in 100)

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

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

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

Seek medical advice immediately:

If the above signs of allergy spread to other parts of your body, or

If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty breathing; have a rapid heart beat; feel dizzy.

You may have a very rare serious allergic reaction to NovoRapid® or one of its ingredients (called a generalized allergic reaction). See also the warning in *'Before you use NovoRapid®'*.

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

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

Rarely reported side effects

(less than 1 in 1,000)

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.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, Diabetes Nurse Educator or your pharmacist.

HOW TO STORE IT

How to store NovoRapid® [Penfill®]

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 - 10°C, in the original package, away from the freezer section. 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®] that is not being used is to be stored in the refrigerator between 2°C - 10°C, not in or too near the freezer section or 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) for up to 4 weeks.

NovoRapid® should be protected from excessive heat and sunlight.

Do not use NovoRapid® after the expiry date printed on the label and carton. The date refers to the last day of the month.

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

REPORTING SUSPECTED SIDE EFFECTS

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 1-866-234-2345

By toll-free fax: 1-866-678-6789

Online: www.healthcanada.gc.ca/medeffect

By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:

Canada Vigilance National Office Marketed Health Products Safety and Effectiveness
Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

Note: Should you require information related to the management of the side effect, please contact your healthcare provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

What NovoRapid[®] [vial / Penfill[®]] looks like and package content

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

NovoRapid[®] Penfill[®] comes as a clear, colourless, aqueous solution in packages of 5 cartridges 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.

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Novo Nordisk A/S

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NovoRapid[®] - Product Monograph

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containing Novo Nordisk Canada in. at 1-800-465-4334.**

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