

PRODUCT MONOGRAPH

Schedule D

**NovoRapid<sup>®</sup>**

Insulin Aspart

Solution for Injection

100 Units/mL

Professed Standard

Antidiabetic Agent

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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

- Hypoglycaemia is the most common adverse effect of insulin products. As with all insulin products the timing of hypoglycaemia may differ. Glucose monitoring shall be performed for all patients with Diabetes Mellitus treated with insulins. (see HYPOGLYCEMIA AND TREATMENT OF OVERDOSAGE)
- Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma or even death. (see ENDOCRINE AND METABOLISM – HYPOGLYCEMIA)
- Any transfer of insulin products should be made cautiously and only under medical supervision. (see WARNINGS AND PRECAUTIONS)
- Some insulin products are short-acting insulin and are known for their rapid onset and short duration of action. The injection of such insulin products should immediately be followed by a meal (within 5 to 10 minutes or given immediately after the meal. (see DOSAGE AND ADMINISTRATION)
- Short-acting insulins should be combined with a longer-acting insulin or insulin infusion pump therapy to maintain adequate glucose control. (see DOSAGE AND ADMINISTRATION)
- Insulin products shall not be mixed with any other insulin unless clearly indicated and done under medical supervision. (see WARNINGS AND PRECAUTIONS)
- Insulin products shall not be used if it is not waterclear and colourless or if it has formed a deposit of solid particles on the wall of the vial or cartridge. (see DOSAGE AND ADMINISTRATION)

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

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

### **General**

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

NovoRapid® differs from regular human insulin by its rapid onset and shorter duration of action. As a result of the fast onset of action, the injection of NovoRapid® should immediately be followed by a meal. As a result of the short duration of action of NovoRapid®, patients with diabetes may also require a longer-acting insulin to maintain adequate glucose control.

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

Thiazolidinediones (TZDs), alone or in combination with other antidiabetic agents (including Insulin), can cause heart failure and oedema. The combination of Insulin with a TZD is not indicated for the treatment of Type 2 Diabetes Mellitus. Please refer to the respective TZD product monograph WARNINGS AND PRECAUTIONS information when the use of these drugs in combination with any insulin, including NovoRapid<sup>®</sup>, is contemplated.

## **Endocrine and Metabolism**

### **Hypoglycemia**

As with other insulins, hypoglycemia is the most common adverse effect of insulin therapy, including NovoRapid<sup>®</sup>. Such reactions following treatment with NovoRapid<sup>®</sup> 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.

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of NovoRapid<sup>®</sup>. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.

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

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

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

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

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

Glucose monitoring is recommended for all patients with diabetes.

### **Hyperglycemia**

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

lethal.

### **Hepatic/Biliary/Pancreas**

The pharmacokinetics of NovoRapid<sup>®</sup> did not change in patients with mild (Mean Child Pugh Score: 5.7), moderate (Mean Child Pugh Score: 7.3) or severe (Mean Child Pugh Score: 10.2) hepatic impairment as compared to subjects with normal hepatic function (Mean Child Pugh Score: 0). As with other insulins, NovoRapid<sup>®</sup> 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**

#### **Local allergic reaction**

As with any insulin therapy, injection site reactions may occur and include pain, redness, itching, hives, swelling, bruising and inflammation. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of NovoRapid<sup>®</sup>.

#### **Systemic Allergic Reaction**

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

#### **Antibody production**

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

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<sup>®</sup> compared to human insulin, cross-reacting antibody levels returned to baseline levels in the NovoRapid<sup>®</sup> 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<sup>®</sup> (n=157) during pregnancy in patients with type 1 diabetes, mean levels of antibodies specific to NovoRapid<sup>®</sup> were low (<3%). Variability between subjects was up to 14% for NovoRapid<sup>®</sup>. The majority of antibodies were cross reacting. There was no observable increase in antibodies with NovoRapid<sup>®</sup> treatment from baseline to the end of the third trimester.

Similar observations were found in cord blood. Mean levels of antibodies specific to NovoRapid<sup>®</sup> 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.

### **Carcinogenesis and Mutagenesis**

See PART II: SCIENTIFIC INFORMATION – TOXICOLOGY

### **Renal**

The pharmacokinetics of NovoRapid® did not change in patients with mild (mean  $Cl_{cr}$  60.0 mL min<sup>-1</sup>), moderate (mean  $Cl_{cr}$ : 35.7 mL min<sup>-1</sup>) and severe (mean  $Cl_{cr}$ : 23.5 mL min<sup>-1</sup>) renal impairment as compared to patient with normal renal function ( $Cl_{cr}$ : > 99.8 mL min<sup>-1</sup>). The degree of renal impairment does not affect the pharmacokinetics variable of NovoRapid®. As with other insulins, NovoRapid® requirement may be reduced in patients with renal impairment. NovoRapid® requirement may need to be adjusted in patients with severe renal impairment.

A single dose pharmacokinetic study of insulin aspart in 18 subjects with type 1 diabetes and with renal function ranging from normal to severely impaired was performed. No apparent effect of creatinine clearance values on AUC,  $C_{max}$ , CL/F and  $t_{max}$  of insulin aspart was found. Data were limited in 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 offspring of patients treated with NovoRapid® were one each of central nervous system anomaly, ankyloglossia and fetal disorders.

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

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

See also WARNINGS AND PRECAUTIONS, 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.

## **Special Populations**

**Pregnant Women:** NovoRapid<sup>®</sup> 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<sup>®</sup>. 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 NFORMAITON, CLINCIAL 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<sup>®</sup>.

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

**Geriatrics:** PK/PD study comparing insulin aspart with soluble human insulin was performed in 19 elderly patients with type 2 diabetes. The relative differences in the pharmacodynamic properties between insulin apart 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<sup>®</sup> for up to 6 months. No differences in dose, efficacy or adverse events were observed between these patients and younger population.

**Pediatrics (2 - 17 years of age):** The pharmacokinetic properties of NovoRapid<sup>®</sup> (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<sup>®</sup> and regular human insulin correlated well with those in healthy adult subjects and type 1 diabetic adults.

The efficacy and safety of NovoRapid<sup>®</sup> 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<sup>®</sup>, 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<sup>®</sup> in adults with type 1 diabetes. In addition, as compared to regular human insulin, NovoRapid<sup>®</sup> 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 mean 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:  $10.2 \pm 4.5$  mmol/L vs.  $11.2 \pm 4.7$  mmol/L, respectively;  $p=0.009$ ; dinner:  $10.5 \pm 4.4$  mmol/L vs.  $11.6 \pm 4.8$  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.

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

**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  $40\text{kg/m}^2$  were treated with NovoRapid®. No difference was observed in efficacy and safety compared to leaner patients.

**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

#### **Transferring Patients from Other Insulins:**

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

#### **Mixing of insulins:**

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

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.

### **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 a patient is pregnant, careful monitoring of the patient is required throughout pregnancy. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

Adverse reactions observed in patients using NovoRapid® are mainly due to the pharmacologic effect of insulin. The most frequently seen undesirable effect in insulin-treated patients is change in blood glucose levels. From clinical investigations, it is known that major 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>: 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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**

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

### **Drug-Drug Interactions**

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

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

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

Octreotide/lanreotide may either increase or decrease insulin requirements.

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

### **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/m<sup>2</sup> were treated with NovoRapid®. No difference was observed in efficacy and safety compared to leaner patients.

Patients should be informed about potential advantages and disadvantages of NovoRapid® (insulin

aspart) therapy including the possible side effects. Patients should also be offered continued education and advice on insulin therapies, life-style management, self-monitoring, complications of insulin therapy, timing of dosage, instruction for use of injection devices and storage of insulin.

The need for regular blood glucose self-monitoring should be considered when using NovoRapid<sup>®</sup> to obtain optimal glycemic control.

Alcohol may intensify or reduce the hypoglycemic effect of insulin.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

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

Dosage of NovoRapid<sup>®</sup> 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<sup>®</sup> and the remainder provided by an intermediate-acting or long-acting insulin.

The dosing of NovoRapid<sup>®</sup> 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<sup>®</sup> (insulin aspart) is administered subcutaneously by injection in the abdominal wall, the thigh, the upper arm, the deltoid region or the gluteal region. Injection sites should be rotated within the same region. NovoRapid<sup>®</sup> 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<sup>®</sup> if it has become viscous (thickened) or cloudy; use it only if it is clear and colourless. NovoRapid<sup>®</sup> should not be used after its expiration date.

If NovoRapid<sup>®</sup> is mixed with an intermediate-acting or long-acting insulin, NovoRapid<sup>®</sup> should be drawn into the syringe first. The injection should be made immediately after mixing. NovoRapid<sup>®</sup> should not be mixed with long-acting insulin analogue. The effect of mixing NovoRapid<sup>®</sup> with either animal-source insulins or human insulin preparations produced by other manufacturers have not been studied. This practice is not recommended.

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

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

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

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

## **HYPOGLYCEMIA AND OVERDOSAGE**

Hypoglycemia may occur as a result of an excessive dose of insulin relative to food intake, energy expenditure, or both. Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia. Symptoms of hypoglycemia may occur suddenly. They may include cold sweat, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may be fatal.

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

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

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

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

The primary activity of 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. Furthermore, postprandial glucose control is an independent risk factor for morbidity and mortality in diabetics. This has been demonstrated with regard to overall mortality and cardiovascular disease and death. Since cardiovascular disease is the most frequent cause of death in a diabetic population, control of postprandial glucose levels is now recognized as an important clinical endpoint of successful diabetic therapy.

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

### **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.

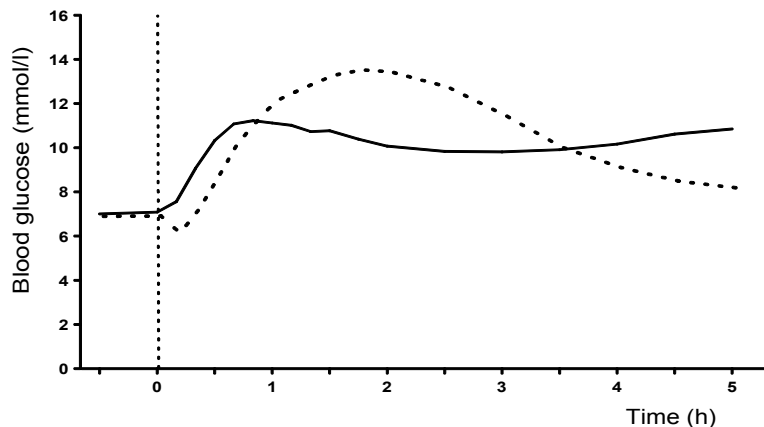


Fig. 1 Mean blood glucose levels following a single pre-meal subcutaneous dose (0.15U/kg) of NovoRapid® injected immediately before a meal (solid line) or regular human insulin administered 30 minutes before a meal (hatched line) in 22 patients with type 1 diabetes.

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<sup>®</sup> showed similar long-term glucose control compared to soluble human insulin.

**Pharmacokinetics**

In NovoRapid<sup>®</sup> 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<sup>®</sup> 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  $492 \pm 256$  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  $C_{max}$  ( $352 \pm 240$  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<sup>®</sup> than for soluble human insulin, where the intra-individual variability in  $C_{max}$  for NovoRapid<sup>®</sup> is larger.

Reduced renal or hepatic function does not alter the pharmacokinetics of NovoRapid<sup>®</sup>.

**Absorption:** NovoRapid<sup>®</sup> (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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> versus 80 to 120 minutes for regular human insulin. The intra-individual variability in time to maximum concentration was significantly less for NovoRapid<sup>®</sup> than for regular human insulin.

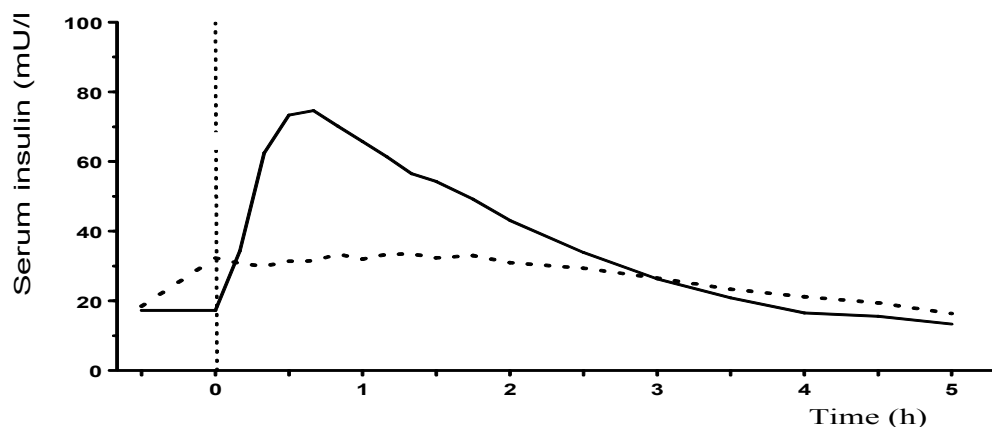


Fig 2 Mean serum insulin concentration following a single pre-meal subcutaneous dose (0.15U/kg body weight) of NovoRapid<sup>®</sup> injected immediately before a meal (solid line) or regular human insulin administered subcutaneously 30 minutes before a meal (hatched line) in 22 patients with type 1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

The pharmacokinetics following a single 0.15 U/kg dose of NovoRapid<sup>®</sup> 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<sup>®</sup> was rapidly absorbed after s.c. administration. There was a significant difference between  $C_{max}$  for NovoRapid<sup>®</sup> 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  $C_{max}$ ,  $352 \pm 240$  pmol/l, and later  $t_{max}$ , 60 minutes.

In healthy subjects, the pharmacokinetic differences between NovoRapid<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> than with regular human insulin.

The extent of absorption (AUC) and  $t_{max(ins)}$  for NovoRapid<sup>®</sup> were found to be independent of injection site when NovoRapid<sup>®</sup> was administered subcutaneously in the abdomen, deltoid, or thigh. However,  $C_{max(ins)}$  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<sup>®</sup>, significantly improved long-term metabolic control was obtained compared to regular human insulin after 6 months treatment, the values being 7.780.03% for NovoRapid<sup>®</sup> and 7.930.05% ( $p < 0.01$ ) for regular human insulin in one trial and correspondingly 7.880.03% and 8.000.04% ( $p < 0.02$ ) 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<sup>®</sup> in a meal-related regimen for 6 months, the pharmacodynamic properties of NovoRapid<sup>®</sup> 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<sup>®</sup> are assumed to be natural amino acids and peptides, which are subsequently incorporated into host proteins or metabolised, as is the case with human insulin. A number of cleavage (hydrolysis) sites on the human insulin molecule have been proposed; none of the insulin metabolites formed following cleavage are active.

**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<sup>®</sup> is reflected in the return of NovoRapid<sup>®</sup> concentrations to pre-dosing levels within 4 hours after dosing.

### **Special Populations and Conditions**

**Pediatrics:** The pharmacokinetic properties of NovoRapid<sup>®</sup> (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<sup>®</sup> 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<sup>®</sup>.

**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<sup>®</sup> pharmacokinetic parameter. Careful glucose monitoring and dose adjustments of insulin, including NovoRapid<sup>®</sup>, 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<sup>®</sup> 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<sub>max</sub> of NovoRapid<sup>®</sup> 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<sup>®</sup> on AUC and C<sub>max</sub> of NovoRapid<sup>®</sup> 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<sup>®</sup>, may be necessary in patients with renal dysfunction. See WARNINGS AND PRECAUTIONS, Renal.

## STORAGE AND STABILITY

NovoRapid<sup>®</sup> (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. In order to protect from light NovoRapid<sup>®</sup> should be kept in the outer carton.

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

NovoRapid<sup>®</sup> should not be used after the expiry date printed on the package.

NovoRapid<sup>®</sup> which has been frozen must not be used.

## SPECIAL HANDLING INSTRUCTIONS

Penfill<sup>®</sup>: Needles and NovoRapid<sup>®</sup> Penfill<sup>®</sup> must not be shared. The cartridge must not be refilled.

NovoRapid<sup>®</sup> must not be used if it does not appear clear and colourless.

NovoRapid<sup>®</sup> which has been frozen must not be used.

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

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

Penfill<sup>®</sup>: In case of emergency in current NovoRapid<sup>®</sup> users (hospitalisation or insulin pen malfunction), NovoRapid<sup>®</sup> can be

withdrawn with an U100 insulin syringe from the cartridge.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

NovoRapid<sup>®</sup> (insulin aspart) is available in 10 mL vials and in 3 mL Penfill<sup>®</sup> cartridges.

NovoRapid<sup>®</sup> Penfill<sup>®</sup> cartridges are designed for use with Novo Nordisk Insulin Delivery Devices, NovoFine<sup>®</sup> and NovoTwist<sup>®</sup> needles.

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

Pack size for vial is 1 x 10 mL.

Pack sizes for all other presentations include 1 x 3 mL, 5 x 3 mL, and 10 x 3 mL.

**Non-medicinal ingredients** : disodium phosphate dihydrate, glycerol, metacresol, phenol, sodium chloride, water for injection and zinc chloride solution. Sodium hydroxide 2N and/or hydrochloric acid may be added to adjust the pH.



## 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. 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  $-1.46 \text{ mmol/L}$  in one trial and  $-1.15 \text{ mmol/L}$  in the other;  $p < 0.0001$ ).

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

### **Type 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 [ $n=118$ ]<sup>4</sup> 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. 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 <sub>Pregnant</sub>

Number of subjects	Pregnant at Screening			Pregnant after Screening			ITT Pregnant		
	P	N	%	P	N	%	P	N	%
	113			44			157		
Visit P2 (week 12)									
A <sub>1c</sub> ≤6.0%	108	36	33.3	31	9	29.0	*	*	*
A <sub>1c</sub> ≤6.5%	108	70	64.8	31	21	67.7	*	*	*
A <sub>1c</sub> ≤7.0%	108	98	90.7	31	26	83.9	*	*	*
Visit P3 (week 24)									
A <sub>1c</sub> ≤6.0%	102	66	64.7	31	13	41.9	133	79	59.4
A <sub>1c</sub> ≤6.5%	102	83	81.4	31	27	87.1	133	110	82.7
A <sub>1c</sub> ≤7.0%	102	96	94.1	31	30	96.8	133	126	94.7
Visit P4 (week 36)									
A <sub>1c</sub> ≤6.0%	96	53	55.2	26	7	26.9	122	60	49.2
A <sub>1c</sub> ≤6.5%	96	77	80.2	26	18	69.2	122	95	77.9
A <sub>1c</sub> ≤7.0%	96	90	93.8	26	26	100.0	122	116	95.1
Follow-up Visit (6 weeks post partum)									
A <sub>1c</sub> ≤6.0%	104	35	33.7	36	8	22.2	140	43	30.7
A <sub>1c</sub> ≤6.5%	104	58	55.8	36	20	55.6	140	78	55.7
A <sub>1c</sub> ≤7.0%	104	80	76.9	36	26	72.2	140	106	75.7

P: Number of subjects with a A<sub>1c</sub> measurement at the actual visit

N: Number of subjects with a A<sub>1c</sub> measurement having the given value at the actual visit

?: Proportion of subjects with a A<sub>1c</sub> 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.

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 apart (IAsp) and single 0.3 U/kg s.c. dose of soluble human insulin (HI) in 19 patients aged 65-83 years (mean age 70 years). 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± 0.05% vs 8.11± 0.05% (95% CI; -0.34 to -0.10, p<0.001), respectively. In addition, the overall mean postprandial plasma glucose was significantly lower with the combination NovoRapid®/ detemir when compared to regular human insulin/ NPH (7.81 mmol/L vs 7.87 mmol/L, respectively; p<0.001) with significant less intra-individual variability in plasma glucose (p < 0.001). This improvement of glycemic control was accompanied with a significant decrease in the risk of nocturnal hypoglycemic events (relative risk decreased by 55%; 95% CI 0.35 - 0.58; p<0.001) and a significant decrease in body weight (p<0.001).

**Hypoglycemia:** In a 16-week double-blind, randomized, multinational, crossover study with type 1 diabetes patients (n= 156, A1C ≤ 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 I NovoRapid® than with regular human insulin (1.3 vs 3.4% of patients, respectively;  $p<0.005$ ).

## 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
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<b>Test</b>	<b>Insulin Aspart/ Human Insulin(HI)</b>	<b>Results</b>
<b>Irwin Observation Test, mice</b>	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No difference from human insulin was observed
<b>Locomotor Activity, rats</b>	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No consistent effect
<b>Rotarod Performance, mice</b>	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No effects
<b>Hexobarbital induced sleeping time, mice</b>	1,10 or 100 U/kg i.v. HI 100 IU/kg IV	No difference from human insulin was observed
<b>Ethanol induced sleeping time, mice</b>	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No difference from human insulin was observed
<b>Anti-convulsant activity, mice</b>	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No effects
<b>Pro-convulsant activity, mice</b>	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No effects
<b>Analgesic effect on acetic acid induced writhing</b>	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No effects
<b>Effects on body temperature</b>	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No effects
<b>Isolated guinea-pig ileum</b>	3.6, 36 or 360 mU/ml HI: 360 mIU/ml	No effects
<b>Autonomic nervous system in anaesthetised cat</b>	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
<b>Cardiovascular and Respiratory Systems in anaesthetised rat</b>	1,10 and 100 U/kg IV, HI: 1,10 and 100 IU/kg IV	No effects
<b>Cardiovascular and Respiratory Systems in anaesthetised pig</b>	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
<b>Gastrointestinal Motility in Mice</b>	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No effects

Test	Insulin Aspart/ Human Insulin(HI)	Results
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 type1 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.
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	<b>Top dose levels</b> 100 bid for 24 weeks, 50 bid weeks 25-26, 100 od weeks 27-37, 75 od from week 38-52.  <b>Lower dose levels</b> 5 and 25U/kg/bid for 26 weeks 10 and 50 od for 27-52 weeks. Controls.	Hypoglycemia, increased food and water consumption and weight gain. Excess of mammary tumours in high dose females.
Rat	Sprague-Dawley	4 Groups 20F	SC	52 weeks	200 per drug substance. Insulin aspart, human insulin, control.	Mammary tumour-incidence higher in insulin aspart group equal to human insulin both being higher than controls.
Dog	Beagle	4 groups	SC	4weeks (+ 4	0, 0.25, 0.5,	Hypoglycaemia.

Species	Strain	Number of groups and size	Dosing Method	Duration (Weeks)	Dose level (U/kg/day)	Results
		3M, 3F/group, main 1M, 1F in groups 1 & 4 reversibility assessment		week recovery in groups 1 & 4)	1.0 bid	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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