

PRODUCT MONOGRAPH

NovoRapid[®]

(Insulin Aspart)

Solution for injection

Professed Standard

NovoMix[®] 30

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

Suspension for injection

Professed Standard

Therapeutic Classification

Antidiabetic Agent

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Date of Approval

February 25, 2005

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ACTION AND CLINICAL PHARMACOLOGY

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.

NovoMix® 30 (30% soluble insulin aspart and 70% insulin aspart protamine crystals) is a dual-release human insulin analogue suspension containing 30% soluble insulin aspart and 70% insulin aspart protamine crystals. The rapid absorption characteristics of **NovoRapid®** are maintained by **NovoMix® 30**. The insulin aspart in the soluble component of **NovoMix® 30** is absorbed more rapidly from the subcutaneous layer than regular human insulin. The remaining 70% is in crystalline form as insulin aspart protamine which has a prolonged absorption profile after subcutaneous injection.

The primary activity of **NovoRapid®** and **NovoMix® 30** is the regulation of glucose metabolism. Insulins, including **NovoRapid®** and **NovoMix® 30**, bind to the insulin receptors on muscle and fat cells and lower blood glucose by facilitating the cellular uptake of glucose - and simultaneously inhibit the output of glucose from the liver.

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. Similarly, the effect of **NovoMix® 30** is more rapid in onset compared to biphasic human insulin 30/70 (i.e. **Novolin®** ge 30/70, insulin, human biosynthetic) due to the faster absorption of the soluble component after subcutaneous injection.

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 postprandial variability in blood glucose concentration.

Pharmacokinetics

Bioavailability and Absorption of **NovoRapid®**

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 insulin¹.

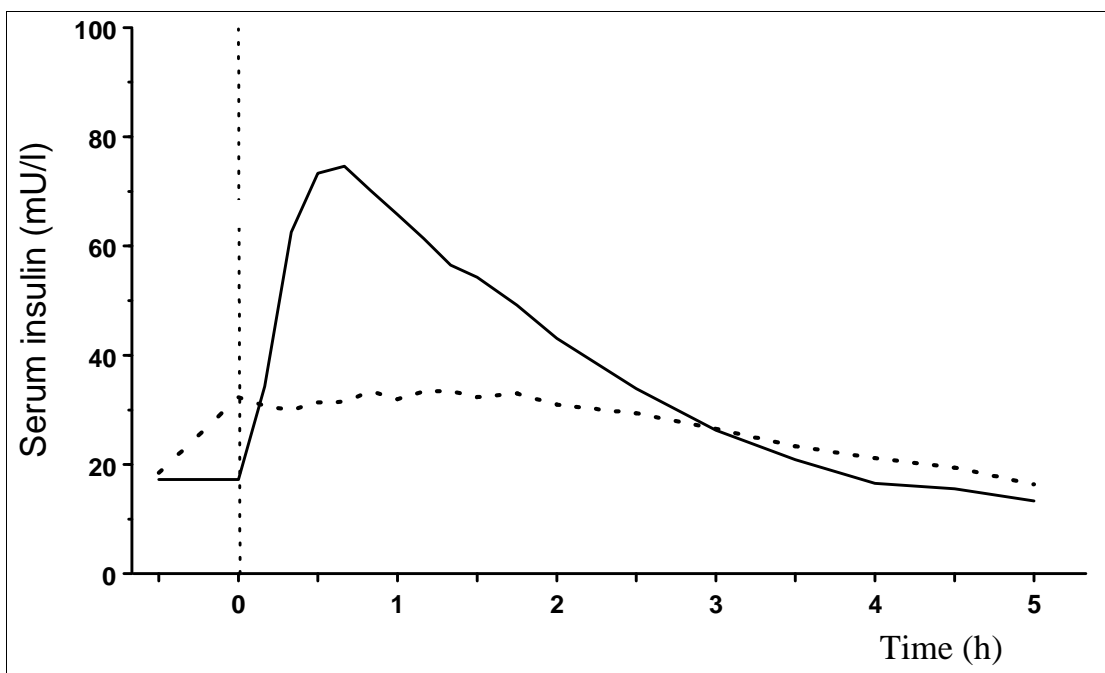


Fig 1. Mean serum insulin concentration following a single pre-meal subcutaneous dose (0.15U/kg body weight) of **NovoRapid®** injected immediately before a meal (solid line) or regular human insulin administered subcutaneously 30 minutes before a meal (hatched line) in 22 patients with type 1 diabetes.

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 1 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).

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

Bioavailability and Absorption of NovoMix® 30:

The rapid absorption characteristics of **NovoRapid**® are maintained by **NovoMix**® 30. The insulin aspart in the soluble component of **NovoMix**® 30 is absorbed more rapidly from the subcutaneous layer than regular soluble human insulin. The remaining 70% is in crystalline form as insulin aspart protamine that has a prolonged absorption profile after subcutaneous injection.

The relative bioavailability of **NovoMix**® 30 compared to premixed human insulin 30/70 indicates that they are absorbed to similar degrees.

The maximum serum insulin concentration (C_{max}) for **NovoMix**® 30 is, on average, 50% higher than with biphasic human insulin 30/70 ($p=0.000$). The time to maximum concentration (T_{max}) is, on average, half that for biphasic human insulin 30/70 ($p=0.000$). In healthy volunteers, a mean maximum serum concentration of 23.4 ± 5.3 mU/L was reached about 60 minutes after a subcutaneous dose of 0.2 U/kg body weight versus 15.5 ± 3.7 mU/L at about 130 minutes for biphasic human insulin 30/70.² The mean half life ($t_{1/2}$) of **NovoMix**® 30, reflecting the absorption rate of the protamine bound fraction, was about 8-9 hours. Serum insulin levels returned to baseline about 15-18 hours after a subcutaneous dose. In type 2 diabetic patients, the maximum concentration was reached about 95 minutes after dosing.³

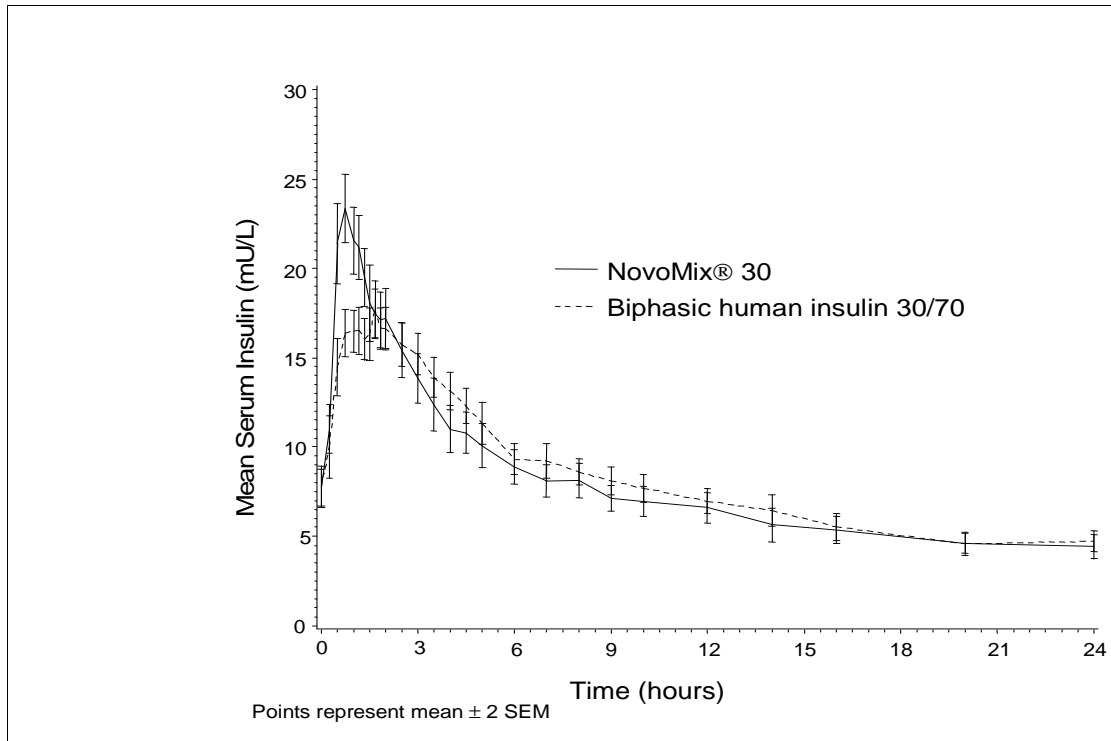
Pharmacokinetic Profiles of **NovoMix® 30** and biphasic human insulin 30/70

Fig. 2. Mean serum insulin concentration following a single subcutaneous dose (0.2U/kg body weight) of **NovoMix® 30** (solid line) and biphasic human insulin 30/70 (hatched line) in healthy subjects

Distribution and Elimination:

Insulin aspart has a low binding to plasma proteins, 0-9%. After subcutaneous administration, insulin aspart was more rapidly eliminated than regular human insulin with an average apparent half life of 81 minutes compared to 141 minutes for regular human insulin.

Pharmacodynamics

NovoRapid®

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 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. 3). 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.

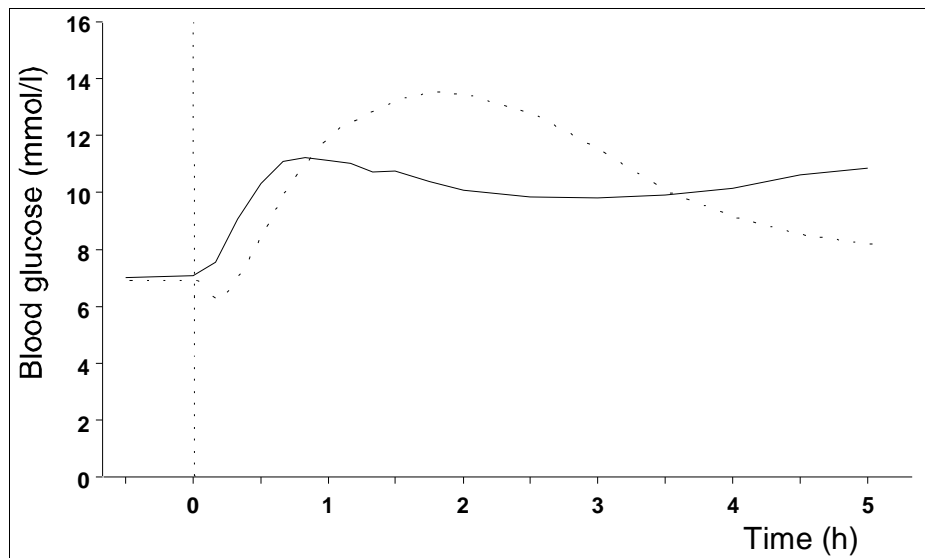


Fig. 3. Mean blood glucose levels following a single pre-meal subcutaneous dose (0.15U/kg) of **NovoRapid**® injected immediately before a meal (solid line) or regular human insulin administered 30 minutes before a meal (hatched line) in 22 patients with type 1 diabetes.

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 ($p = 0.015$).

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 insulin⁴.

Long-term metabolic control, assessed by HbA_{1c} 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).

NovoMix® 30

NovoMix® 30 (30% soluble insulin aspart and 70% insulin aspart protamine crystals) is a dual-release human insulin analogue suspension containing 30% soluble insulin aspart. This has a rapid onset of action, thus allowing it to be given closer to a meal when compared to soluble human insulin. The crystalline phase (70%) consists of insulin aspart protamine, which has an activity profile similar to that of human NPH insulin.

The pharmacodynamic response to a single dose of 0.3 U/kg **NovoMix® 30** and premixed human insulin 30/70 was investigated in 24 healthy subjects using the hyperinsulinaemic euglycemic clamp method*. **NovoMix® 30** shows a significantly greater metabolic effect in the first 4 hours after subcutaneous injection than the premixed human insulin 30/70 (see Figure 4 below)⁵. When **NovoMix® 30** is injected subcutaneously, the onset of action will occur within 10 to 20 minutes of injection. The maximum effect is exerted between 1 and 4 hours after injection. The duration of action is up to 24 hours

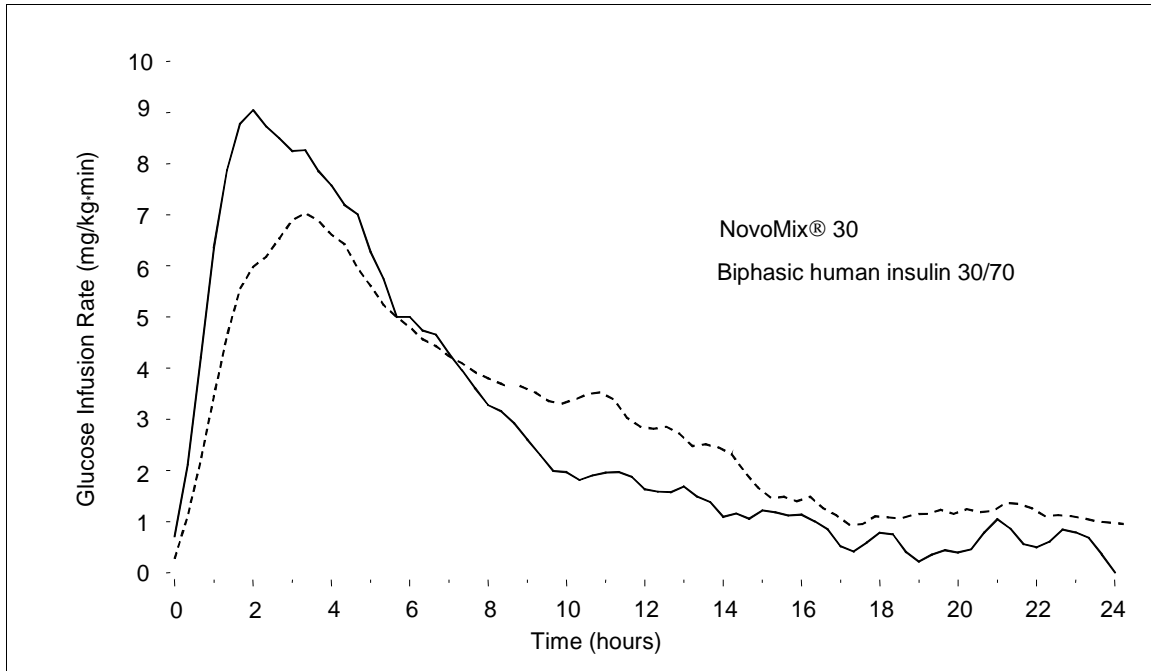


Fig. 4 Pharmacodynamic activity profile of NovoMix® 30 and biphasic human insulin 30/70 in healthy subjects

In a randomized, double-blind, two-way cross-over trial comparing **NovoMix® 30** and biphasic human insulin 30/70 in patients with type 2 diabetes, the therapeutic response was evaluated following two 2-week treatment periods where insulin was administered in a twice daily dose regimen; immediately before breakfast and dinner. The shape of the 24-hour total serum glucose concentration-time profiles were statistically significantly different between treatments over time (see Figure 5 below). Although there was no difference detected between treatments with respect to average serum glucose levels over 24 hours, the estimated mean time-action curves shown below indicate that postprandial glucose control was superior with **NovoMix® 30** compared to biphasic human insulin 30/70, following dinner and breakfast but higher after lunch.³

Estimated Mean 24-hour Serum Glucose Profiles

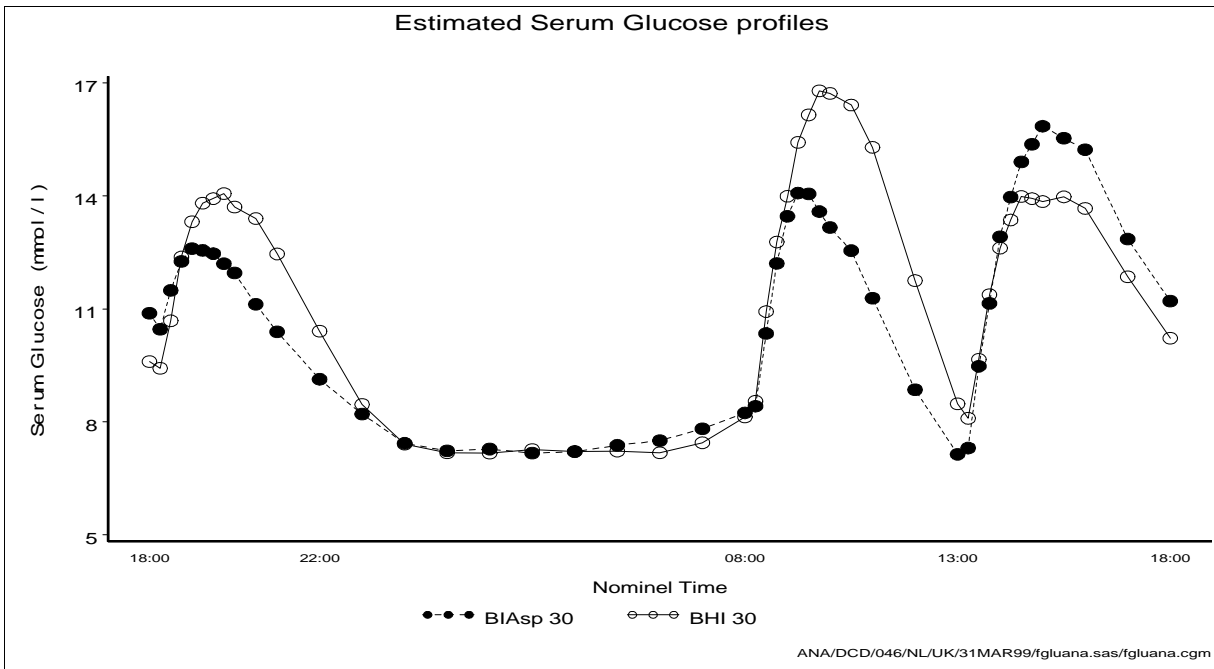


Fig. 5 Estimated serum glucose levels following twice daily injection (immediately before breakfast and dinner) of NovoMix® 30 (BIAsp 30) or biphasic human insulin (BHI 30) in 13 patients with type 2 diabetes.

In a 3 month, multicentre, open-labelled, randomized, parallel group study, **NovoMix® 30** was as effective as biphasic human insulin 30/70 (**Novolin® ge 30/70**) in long-term glycemic control, based on HbA_{1c} levels.⁶ Mealtime blood glucose increment averaged over the three main meals was statistically significantly different (29% lower) in the **NovoMix® 30** group ($p < 0.02$) and statistically significant differences (approximately 1 mmol/l lower) were observed in mean blood glucose levels after breakfast, before lunch, after dinner and at bedtime ($p < 0.02-0.05$). Improvements in postprandial glycemic control did not increase the risk of hypoglycemia. Patients wishing to continue in an extension of this study were followed for an additional 21 month period on either **NovoMix® 30** or **Novolin® ge 30/70**. At the end of the 24 month period of treatment, glycemic control, as measured by HbA_{1c}, was similar in the two groups.⁷

With similar levels of glycemic control (as assessed by HbA_{1c}), the number and rate of hypoglycemic episodes was similar in patients with Type 1 diabetes. However, for patients with type 2 diabetes, those treated with **NovoMix® 30** had a lower frequency of major hypoglycemia than those receiving **Novolin® ge 30/70** and during the last six months of the study, no patients treated with **NovoMix® 30** experienced major hypoglycemia.⁷

In a clinical trial, 61 subjects with type 2 diabetes received a single dose of **NovoMix® 30**, **Humalog® Mix25** and **Novolin® ge 30/70** (insulin, human biosynthetic) on three separate occasions in a cross-over trial. Postprandial glycemic control, as assessed by the 5-hour post meal serum glucose excursion was statistically significantly improved (a 10% reduction, $p < 0.05$) with **NovoMix® 30** over **Humalog® Mix25** and **Novolin® ge 30/70** (a 17% reduction, $p < 0.001$).⁸ For **NovoMix® 30** versus **Novolin® ge 30/70**, maximum glucose concentration was reduced and occurred earlier. Compared to **Humalog® Mix25** there was a shorter time to maximum glucose concentration.⁸

One hundred and fifty-one type 2 patients inadequately treated with oral diabetes medication (metformin with/without insulin secretagogues) were entered into a clinical trial. During the first 4 weeks of the trial, patients were titrated to target with metformin only. Those patients who did not achieve fasting glycemic levels within the target range of 5 - 7 mmol/l (n = 140) were initiated on insulin therapy in a randomized fashion to receive one of three insulin treatment regimens once a day in combination with the metformin therapy: **NovoMix® 30** (at dinner), **Novolin®ge 30/70** (at dinner) or **Novolin®ge NPH** (before bed). There were no statistically significant differences between treatment groups for long term glycemic control; mean HbA_{1c} levels were reduced from baseline by 1.1 - 1.3% with 12 weeks of treatment. There was no significant difference in reporting of hypoglycemic events among the three groups although fewer patients reported nocturnal hypoglycemic events in the **NovoMix® 30** group than in the other groups. At the end of the study, the final fasting plasma glucose fell within target range (5-7 mmol/l) for 9 subjects in the **NovoMix® 30** group, 9 subjects in the **Novolin®ge NPH** group and 8 subjects in the **Novolin®ge 30/70** group. The mean decrease in HbA_{1c} values experienced by these subjects (-2.3%, -1.9% and -1.8% respectively) were greater than observed for the total study population.⁹

Metformin-treated patients with type 2 diabetes (n = 341) were randomized to receive **NovoMix® 30** monotherapy BID, **NovoMix® 30** BID with existing metformin or sulphonylurea therapy with existing metformin. In the total population, the mean difference in HbA_{1c} levels was statistically significant only for subjects receiving **NovoMix® 30** plus metformin versus **NovoMix® 30** monotherapy (p = 0.004). Mean decrease in HbA_{1c} during the study was 1.5 - 1.8% in all groups. In 193 patients with poorly controlled diabetes at the start of the trial (HbA_{1c} < 9.0%), the mean difference in HbA_{1c} was statistically significant in the **NovoMix® 30** plus metformin group versus the **NovoMix® 30** monotherapy group (p = 0.037) and the sulphonylurea plus metformin group (p = 0.033) after 16 weeks of treatment.¹⁰ Mean HbA_{1c} decrease during the study was 1.9 to 2.4% in all groups.

The efficacy and safety of **NovoMix® 30** in **NovoMix® 30 FlexPen®** was compared with **Humalog® Mix25** in **Humalog® Mix25 Pen** in 132 insulin-treated patients with type 2 diabetes in a open-label, two-period crossover design trial. Following a 2-week run-in period on **NovoMix® 30**, patients began the first 12-week treatment period on either **NovoMix® 30** or **Humalog® Mix25**. At the last visit of the first treatment period, the patients completed pen device questionnaires and the WHO Diabetes Treatment Satisfaction Questionnaire (DTSQ) and then changed to the alternate insulin treatment. At the end of the 2nd 12-week treatment period, patients again completed the pen device questionnaires, the DTSQ and a comparative questionnaire asking which device they would prefer to continue to use after the trial. Treatment with **NovoMix® 30** and **Humalog® Mix25** were comparable with respect to HbA_{1c}, prandial blood glucose increment, postprandial blood glucose and episodes of hypoglycemia at the end of the trial. Patient treatment satisfaction, as measured by DTSQ was similar for both groups. For the device specific questionnaires, **NovoMix® 30 FlexPen®** was evaluated as slightly superior to **Humalog® Mix25 Pen** in 15 of 16 device features assessed (all p < 0.001). Approximately 75% of patients preferred to continue with **NovoMix® 30 FlexPen®** after the trial was completed.¹¹

Special populations

Age and Gender

Children and adolescents - 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.

The safety and efficacy of **NovoMix® 30** were compared to biphasic human insulin 30/70 (BHI 30) in a double-blind crossover trial in 54 children, aged 6-12 years. The incidence of all hypoglycemic episodes was significantly lower for **NovoMix® 30** than for BHI 30 by approximately 10%. No safety concerns were raised during the trial. However, after 12 weeks of treatment it could not be demonstrated, that treatment with **NovoMix® 30** was non-inferior to treatment with BHI 30 with respect to HbA_{1c} and serum fructosamine. The data available are inadequate to establish the effectiveness in children.

Geriatrics - 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. The effect of age on the pharmacokinetics and pharmacodynamics of **NovoMix® 30** has not been studied.

Gender - There was no significant difference in pharmacokinetics in a trial of **NovoRapid®** in type 2 diabetic patients. No significant difference in efficacy, as assessed by HbA_{1c}, was found between genders in a trial in type 1 diabetic patients. The effect of gender on the pharmacokinetics and pharmacodynamics of **NovoMix® 30** in diabetic patients has not been studied.

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

Ethnic origin

There was no difference in efficacy in **NovoRapid®** trials in terms of blood glucose control as measured by HbA_{1c} or safety in terms of adverse events between African Americans, Hispanics and Caucasian patients. The effect of ethnic origin on the pharmacokinetics and pharmacodynamics of **NovoMix® 30** has not been studied.

Smoking

The effect of smoking on the pharmacokinetics and pharmacodynamics of **NovoRapid®** or **NovoMix® 30** 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.

INDICATIONS AND CLINICAL USE

NovoRapid® (insulin aspart) is indicated for the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. **NovoRapid®** should normally be used in regimens together with an intermediate or long-acting insulin.

NovoMix® 30 (30% soluble insulin aspart and 70% insulin aspart protamine crystals) is indicated for the treatment of adult patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis.

CONTRAINDICATIONS

NovoRapid® (insulin aspart) and **NovoMix**® 30 (30% soluble insulin aspart and 70% insulin aspart protamine crystals) are contraindicated during episodes of hypoglycemia (see HYPOGLYCEMIA AND OVERDOSAGE) and in patients hypersensitive to insulin aspart or any of the excipients they contain.

WARNINGS

Insulin aspart differs from regular human insulin by its rapid onset and shorter duration of action. Because of the fast onset of action, the injection of **NovoRapid**® (insulin aspart) or **NovoMix**® 30 (30% soluble insulin aspart and 70% insulin aspart protamine crystals) should immediately be followed by a meal. To avoid possible transmission of disease, a **Penfill**® cartridge must not be used by more than one person.

PRECAUTIONS

General

As with all insulins, the duration of action of **NovoRapid**® (insulin aspart) or **NovoMix**® 30 (30% soluble insulin aspart and 70% insulin aspart protamine crystals) may vary in different individuals or in the same individual according to dose, injection site, blood flow, temperature and level of physical activity.¹²

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 drugs.¹³

Stress or illness may change insulin requirements. In these instances, patients should contact their physician and carefully control their blood glucose.¹²

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 pronounced.¹⁴

Hypoglycemia is the most frequently occurring undesirable effect of insulin therapy. Such reactions following treatment with **NovoRapid**® or **NovoMix**® 30 are mostly mild and easily managed.

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. 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.

Glucose monitoring is recommended for all patients with diabetes.

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).

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 excipients¹⁶. Few local injection site reactions were observed with **NovoRapid®** or **NovoMix® 30** in the clinical development program and there was no difference in frequency when compared to human insulin.

Systemic allergic reaction

Systemic allergic reaction have not been reported during the clinical development of **NovoRapid®** or **NovoMix® 30**. Systemic allergic reactions have rarely occurred with **NovoRapid®** and **NovoMix® 30** as with other insulin treatment. These reactions may be characterized by a generalized rash (with pruritus), shortness of breath, wheezing and drop in blood pressure. Severe cases of generalized allergy including anaphylactic reaction may be life threatening.¹⁶

Antibody production

Insulin antibodies may develop during treatment with insulin. In the clinical development program for **NovoRapid®**, 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. Insulin antibody production was further monitored during the clinical development program for **NovoMix® 30**. A transitory 11.2% increase in cross-reactive antibodies observed during the initial 3 months of treatment with BIAsp 30 in the phase III trial was followed by a significant decrease from month 3 to 12. This decrease was maintained between months 12 and 24, where concentrations were constant at about 5 absolute percentage points above baseline for the type 2 diabetic subjects and 7.02% for the total population (type 1 and 2 diabetic subjects). No relationship between cross-reactive antibody level and metabolic control, insulin dose requirements or adverse events has been observed.¹⁵

Renal impairment

There is no experience of treatment with insulin aspart in patients with renal impairment. As with other insulins, **NovoRapid®** and **NovoMix® 30** requirement may be reduced in patients with renal impairment.

Hepatic impairment

There is no experience of treatment with insulin aspart in patients with hepatic impairment. As with other insulins, **NovoRapid®** and **NovoMix® 30** requirement may need to be adjusted in patients with hepatic impairment.

Use in Women***Teratogenicity***

There is no information on teratogenicity of insulin aspart 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.

Pregnant Women

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**®. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Although there are no clinical studies of the use of **NovoRapid**® or **NovoMix**® 30 in pregnancy, published studies with human insulin suggest that optimizing overall glycemic control, including postprandial control, before conception and during pregnancy improves fetal outcome. Although the fetal complications of maternal hyperglycemia have been well documented, fetal toxicity also has been reported with maternal hypoglycemia. Insulin requirements usually fall during the first trimester and increase during the second and third trimesters. Careful monitoring of the patient is required throughout pregnancy. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.¹⁷

Lactating Women

It is unknown whether **NovoRapid**® or **NovoMix**® 30 are excreted in significant amounts in human milk. For this reason, caution should be exercised when **NovoRapid**® or **NovoMix**® 30 are administered to a nursing mother. Patients with diabetes who are lactating may require adjustments in insulin dose, meal plan or both.

Use in Children

The data available are inadequate to establish the efficacy of **NovoMix**® 30 in children (See Special Populations: Children and Adolescents).

Self-Monitoring of Blood Glucose

As with all insulin therapy the need for regular blood glucose self-monitoring should be considered when using **NovoRapid**® or **NovoMix**® 30 to obtain optimal glycemic control.

Drug Interactions

Concomitant use of other drugs may influence insulin requirements. 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.¹³

Other drugs may increase insulin requirements: oral contraceptives, thiazides, glucocorticosteroids, thyroid hormones, sympathomimetics and danazol. Beta blocking agents may mask the symptoms of hypoglycemia.¹³ Alcohol may intensify and prolong the hypoglycemic effect of insulin.¹³

Transferring Patients from Other Insulins:

When patients are transferred between different types of insulin products, the early warning symptoms of hypoglycaemia may change 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 under strict medical supervision. Changes in strength, brand, type, species (animal, human,

human insulin analogue), and/or method of manufacture may result in the need for a change in dosage. Patients taking **NovoRapid®** or **NovoMix® 30** may need a change in dosage from that used with their usual insulins. If an adjustment is needed, it may be done with the first dose or during the first few weeks or months

Information for patients

Patients should be informed about potential advantages and disadvantages of **NovoRapid®** or **NovoMix® 30** therapy including the possible side effects. Patients should also be offered continued education and advice on insulin therapies, life-style management, self-monitoring, complications of insulin therapy, timing of dosage, instruction for use of injection devices and storage of insulin.¹⁸

The need for regular blood glucose self-monitoring should be considered when using any insulin therapy to obtain optimal glycemic control.

Female patients should be advised to discuss with their physician if they intend to or if they become pregnant.

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 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.

NovoMix® 30 should not be mixed with any other insulin product.

ADVERSE REACTIONS

Clinical trials comparing **NovoRapid®** (insulin aspart) with regular human insulin did not demonstrate any differences in frequency of adverse events between the aspart formulations and their human insulin counterparts.

Adverse events can be categorized into the following areas:

Body as whole: (see PRECAUTIONS).

Skin reactions: (see PRECAUTIONS; local allergic reactions).

Other; Hypoglycemia: (see WARNINGS, PRECAUTIONS and below).

The serious and important Adverse Drug Reactions associated with insulin treatment are events of hypoglycemia, hypoglycemic coma, poor blood glucose control, and the most frequent event hyperglycemia (see Hypoglycemia and Treatment of Overdosage).

The following table provides the distribution of all Adverse Events (greater than 1%) occurring in >1% of subjects in a 24 month study for NovoMix®.

Commonly Report Adverse Events Occurring in >1% of patients				
	BIAsp 30 N = 101		BHI 30 N = 103	
Respiratory System Disorders				
Upper Resp tract infection	46	46%	35	34%
Pharyngitis	16	16%	10	10%
Coughing	12	12%	8	8%
Rhinitis	10	10%	9	9%
Sinusitis	5	5%	3	3%
Bronchitis	4	4%	3	3%
Dyspnoea	2	2%	3	3%
Pneumonia			2	2%
Pulmonary Oedema			2	2%
Chronic obstructive airways disease			2	2%
Central & Peripheral Nervous System Disorders				
Headache	29	29%	17	17%
Sensory disturbance	10	10%	9	12%
Hyporeflexia	9	9%	8	9%
Neuropathy	8	8%	4	8%
Migraine	3	3%	2	4%
Cramps legs	3	3%	3	2%
Dizziness	2	2%	1	3%
Vertigo	2	2%	3	<1%
Neuralgia	1	<1%		3%
Body as a Whole - General Disorders				
Influenza-like symptoms	21	21%	205	19%
Back pain	11	11%	4	5%
Leg pain	5	5%	3	4%
Allergic Reaction	4	4%	1	3%
Headache	4	4%	2	<1%
Fatigue	2	2%	1	2%
Allergy	2	2%	1	<1%
Pain	2	2%		<1%
Malaise	2	2%		
Nasal polyp	2	2%	5	
Chest pain	1	<1%	2	5%
Carpal tunnel syndrome				2%
Gastro-Intestinal System Disorders				
Dyspepsia	13	13%	9	9%
Diarrhea	12	12%	13	13%
Abdominal pain	8	8%	5	5%
Tooth ache	6	6%	4	4%
Nausea	5	5%	7	7%
Gastroenteritis	4	4%	1	<1%

Commonly Report Adverse Events Occurring in >1% of patients				
	BIAsp 30 N = 101		BHI 30 N = 103	
Vomiting	3	3%	9	9%
Constipation	3	3%	4	4%
Gingivitis	2	2%	2	2%
Tooth disorder	2	2%	2	2%
Oesophagitis	2	2%		
Gastritis			4	4%
Gastro-intestinal disorder nos			2	2%
Musculo-Skeletal System Disorders				
Arthralgia	9	9%	6	6%
Skeletal pain	8	8%	7	7%
Back pain	7	7%	3	3%
Myalgia	7	7%	1	<1%
Arthropathy	3	3%	3	3%
Arthritis	2	2%	3	3%
Arthrosis	2	2%	2	2%
Bone disorder	2	2%	1	<1%
Ischias			3	3%
Resistance Mechanism Disorders				
Infection	15	15%	17	17%
Infection fungal	4	4%	4	4%
Moniliasis	3	3%	4	4%
Infection viral	2	2%	2	2%
Abscess	2	2%	1	<1%
Herpes simplex	2	2%		
Infection wound	1	<1%	3	3%
Upper resp tract infection	1	<1%	2	2%
Skin and Appendages Disorders				
Skin disorder	5	5%	4	4%
Rash	4	4%	4	4%
Skin ulceration	3	3%	4	4%
Eczema	3	3%	3	3%
Dermatitis fungal	3	3%		
Urticaria	3	3%		
Hyperkeratosis	2	2%	1	<1%
Seborrhoea	2	2%	1	<1%
Skin dry	2	2%	1	<1%
Pruritus	1	<1%	2	2%
Metabolic and Nutritional Disorders				
Hypercholesterolaemia	7	7%	2	2%
Hyperlipaemia	4	4%	5	5%
Lipid metabolism disorder nos	3	3%		
Diabetes mellitus aggravated	2	2%		
Gout	2	2%		
Weight decrease	2	2%		

Commonly Report Adverse Events Occurring in >1% of patients				
	BIAsp 30 N = 101		BHI 30 N = 103	
Hyperglycaemia	1	<1%	3	3%
Hypoglycaemia	1	<1%	2	2%
Oedema leg				2%
Cardiovascular Disorders, General				
Hypertension	16	16%	14	14%
Cardiac Failure	3	3%	3	3%
Heart Murmur	1	<1%	2	2%
Oedema Dependent			2	2%
Secondary Terms				
Injury accidental	12	12%	15	15%
Vision Disorders				4%
Retinal disorder	5	5%	4	<1%
Conjunctivitis	2	2%	1	<1%
Retinal hemorrhage	2	2%	1	<1%
Vision abnormal	2	2%	1	3%
Eye abnormality			3	
Urinary System Disorders				
Urinary tract infection	5	5%	9	9%
Cystitis	2	2%	2	2%
Albuminuria	2	2%	1	<1%
Haematuria			3	3%
Renal function abnormal			2	2%
Liver and Biliary System Disorders				
Hepatic enzymes increased	4	4%		
Cholecystitis			2	2%
Psychiatric Disorders				
Depression	3	3%	3	3%
Anxiety	2	2%	4	4%
Impotence	2	2%		
Vascular (extracardiac) disorders				
Peripheral ischaemia	3	3%	1	<1%
Vascular disorder	1	<1%	3	3%
Myo Endo Pericardial & Valve Disorders				
Myocardial ischaemia	4	4%		
Angina pectoris	2	2%	3	3%
Coronary artery disorder	1	<1%	2	2%
Myocardial infarction			2	2%
Neoplasm				
Pulmonary carcinoma	2	2%		

Commonly Report Adverse Events Occurring in >1% of patients				
	BIAsp 30 N = 101		BHI 30 N = 103	
Application Site Disorders Fibrous nodule	2	2%		
Reproductive Disorders, Female Dysmenorrhoea	2	2%	2	2%
Heart Rate and Rhythm Disorders Arrhythmia	2	2%	1	<1%
Red Blood Cell Disorders Erythrocytes abnormal AnaemiaSecondary Terms Injury accidental	2	2%	3	3%
Hearing and Vestibular Disorders Earache	2	2%	2	2%

N = Number of subjects with event
% = Proportion of exposed subjects having the event

Other

Small elevations in alkaline phosphatase were observed in patients treated with **NovoRapid®** and **NovoMix® 30** in controlled clinical trials. Some patients initially had normal levels of alkaline phosphatase, which subsequently rose above normal range. There have been no clinical consequences of these findings.

HYPOGLYCEMIA AND TREATMENT OF 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.

DOSAGE AND ADMINISTRATION

Dosage

NovoRapid® (insulin aspart) and **NovoMix**® 30 (30% soluble insulin aspart and 70% insulin aspart protamine crystals) should generally be given immediately before a meal because of the fast onset of action (start of the meal should be not more than 5-10 minutes after injection). When necessary **NovoRapid**® and **NovoMix**® 30 may be given immediately after the meal.

Dosage of any insulin 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. In a premixed insulin regimen, the total daily dose can be provided by **NovoMix**® 30.

The dosing of any insulin should be regularly adjusted according to blood glucose measurements.

New Patients:

Patients being initiated on insulin for the first time can be started on **NovoRapid**® or **NovoMix**® 30 in the same manner as they would be on animal-source or human insulin.

Transfer Patients:

When patients are transferred from other insulin to **NovoRapid**® or **NovoMix**® 30, the change should be made as directed by the physician.

In clinical trials, patients were transferred on a unit to unit basis from regular human insulin to **NovoRapid**® and then the doses of meal-related and basal insulin were changed according to the patients' needs and local practice. Similarly, in clinical trials of **NovoMix**® 30, patients were transferred on a unit to unit basis from human premixed 30/70 or human NPH to **NovoMix**® 30 with doses subsequently adjusted according to individual patient needs.

Administration

NovoRapid® (insulin aspart) and **NovoMix**® 30 (30% soluble insulin aspart and 70% insulin aspart protamine crystals) are administered subcutaneously in the abdominal wall, the thigh, the upper arm or the buttock. Care should be taken to avoid entry into a blood vessel. 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, buttock). As with all insulins, the duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

NovoRapid®

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. 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.

NovoMix® 30

NovoMix® 30 is a white suspension. The carton contains a package leaflet with instructions for use and handling. The necessity of properly resuspending **NovoMix® 30** immediately before use should be stressed to the patient. The resuspended liquid must appear uniformly white and cloudy. **NovoMix® 30** should not be used after it's expiration date. **NovoMix® 30** should not be injected intravenously.

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

PHARMACEUTICAL INFORMATION

Proper Name: Insulin Aspart
 Chemical Name: B28 asp regular human insulin analogue
 Structural Formula: $C_{256}H_{381}N_{65}O_{79}S_6$
 Molecular weight: 5825.8

NovoRapid® (insulin aspart) is homologous with regular human insulin with the exception of a substitution of the amino acid aspartic acid for proline in position B28.

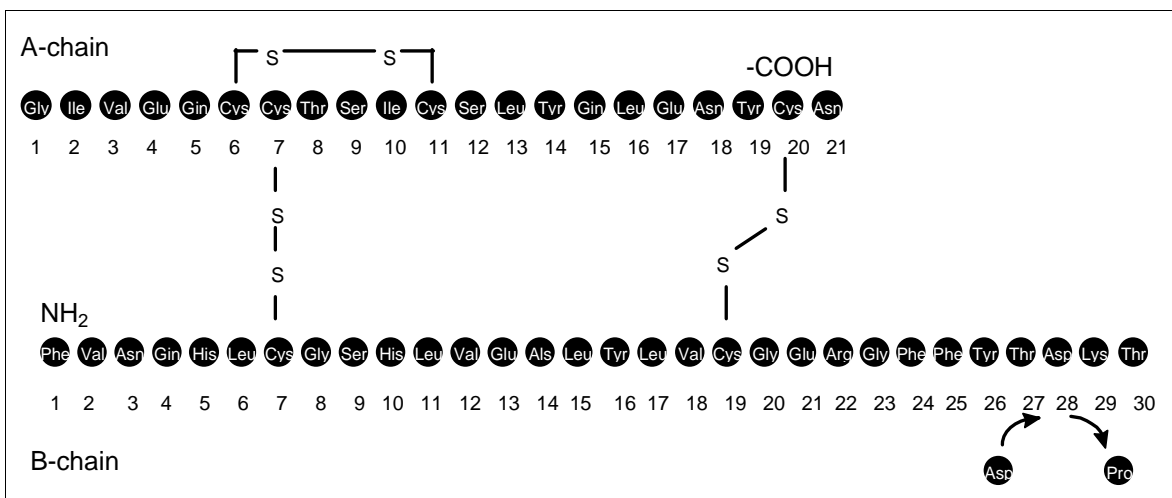


Fig. 6. Structural formula of insulin aspart

NovoRapid® is a sterile, aqueous, clear and colourless solution, that contains insulin aspart (B28 asp regular human insulin analogue) 100 Units/mL, glycerin 16 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 19.6 µg/mL, disodium hydrogen phosphate dihydrate 1.25 mg/mL and sodium chloride 0.58 mg/mL. **NovoRapid®** has a pH of 7.2-7.6.

NovoMix® 30 is a sterile, uniform, white suspension that contains insulin aspart (B28 asp regular human insulin analogue) 100 Units/mL, mannitol 36.4 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 19.6 µg/mL, disodium hydrogen phosphate dihydrate 1.25 mg/mL, sodium chloride 0.58 mg/mL and protamine sulfate 0.33 mg/mL. **NovoMix® 30** has a pH of 7.20-7.44.

STABILITY AND STORAGE RECOMMENDATIONS

NovoRapid® (insulin aspart) and **NovoMix® 30** (30% soluble insulin aspart and 70% insulin aspart protamine crystals) should be stored between 2 and 10°C. Do not freeze. Cartridges and vials in use or carried as a spare may be kept at ambient temperature for up to 4 weeks, but should not be exposed to excessive heat or sunlight.

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

AVAILABILITY OF DOSAGE FORMS

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). **NovoMix® 30** (30% soluble insulin aspart and 70% insulin aspart protamine crystals) is available in 3 mL **Penfill®** cartridges (in cartons of 5 cartridges). All presentations are in a strength of 100 Units of insulin aspart per mL.

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

INFORMATION FOR THE CONSUMER

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

NovoRapid® Patient Insert

What is NovoRapid®?

NovoRapid® is a human insulin analogue manufactured by Novo Nordisk. It is also called insulin aspart. The active substance in **NovoRapid®** is insulin aspart produced by biotechnology.

Why have you been given NovoRapid®?

NovoRapid® is used for the treatment of diabetes mellitus as it reduces the level of sugar in the blood and urine. To control your diabetes, your doctor has prescribed injections of insulin, insulin aspart, or both.

When injected under your skin (subcutaneously), **NovoRapid®** has a rapid onset of effect (10-20 minutes), a maximum effect between 1 and 3 hours and the effect lasts for approximately 5 hours.

Availability of NovoRapid®

NovoRapid® is available in the following formats:

10 mL vial in cartons of 1 vial

3 mL **Penfill®** cartridge

(designed for use with Novo Nordisk Insulin Delivery Devices and **NovoFine®** needles)

Before you take NovoRapid®

You should not take NovoRapid®:

- if your blood sugar is too low (hypoglycemia).
- if you are allergic to **NovoRapid®** or any of the ingredients contained in **NovoRapid®** (check with your doctor or pharmacist if you are not sure)
- if you are not planning to eat immediately after your injection

Dosage

Follow carefully the instructions given by your doctor concerning type of insulin, dose, and time of injection. Any change in insulin should be made cautiously and only under medical supervision. Your insulin requirements may change due to a number of factors (illness, stress, medications, changes in diet or exercise routines, etc.). Follow your doctor's instructions to allow for these changes.

The following can be considered as general guidelines. Consult your doctor for information which is specific to your diabetes.

Can NovoRapid® be taken with other medicines?

A number of drugs are known to influence insulin requirement. Therefore, if you are taking any other medication, please consult your doctor.

What do you have to consider during pregnancy or while breastfeeding?

If you are pregnant or planning pregnancy you should see your doctor immediately to discuss your need for and type of insulin in order to control your diabetes and thereby avoid hyperglycemia (too high blood sugar) and hypoglycemia (too low blood sugar) as these conditions could harm your baby. Breastfeeding while you are taking insulin does not put your baby at risk. Your insulin dosage and diet may, however, need to be adjusted.

Alcohol Use

Alcohol (including beer and wine) may lead to hypoglycemia (too low blood sugar). Therefore be careful when you drink alcohol and never drink alcohol on an empty stomach. Follow your physician's advice regarding diet and alcohol consumption.

What should be done during illness?

Never stop taking insulin if you are ill, as you may need more insulin than normal. This may be especially the case if you have an infection, fever, eat less than usual or vomit. Monitor your blood glucose regularly and adjust your therapy according to your physician's advice.

If you have certain problems with your kidneys or your liver your doctor may lower your insulin dosage.

What about travelling?

The time difference between countries may mean that you have to take your insulin and meals at different times than usual. You should therefore consult your doctor if you are planning to go abroad or travel across time zones.

Is NovoRapid® available in other countries?

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

Proper Use of NovoRapid®**Before using your NovoRapid®**

- Do not use NovoRapid® if it does not appear water-clear and colourless.
- Do not use NovoRapid® after the expiry date printed on the label.
- Do not use NovoRapid® if it has not been stored according to the manufacturer's recommendations.

Before using your NovoRapid® Penfill®

- Before use, check that the Penfill® cartridge is intact (no cracks).
- Do not use Penfill® if any damage is seen or if more of the rubber piston is visible than equal to the width of the white bar code band.

- To avoid possible transmission of disease, a **NovoRapid® Penfill®** cartridge must not be used by more than one person.

General Information on use of NovoRapid®

- Before injection, make sure that you have got the type and strength of insulin prescribed.
- **NovoRapid®** is for injection under the skin (subcutaneously). You will feel the effect more quickly if the insulin is injected into your abdomen. However injections may also be given in your thigh, upper arm or buttock.
- It is recommended that you eat a meal or snack containing carbohydrate within 10 minutes of the injection (start of the meal should be not more than 5 - 10 minutes after injection).
- When necessary **NovoRapid®** may be given immediately after the meal.

Injections

Follow the instructions of your physician or health care professional on how to make injections.

Use of NovoRapid® vials:

If you use only NovoRapid®

- 1 Draw into the syringe the same amount of air as the dose of **NovoRapid®** 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

1. Just before use, roll the longer 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 longer acting insulin. Inject the air into the vial containing the longer acting insulin and pull out the needle.
3. Draw into the syringe the same amount of air as the dose of **NovoRapid®** (clear) insulin analogue. Inject the air into the vial containing **NovoRapid®**. Turn the vial upside down with the syringe in it and draw up the prescribed dose of short acting insulin. Expel any air from the syringe and check that the dose is correct.
4. Push the needle into the vial of longer 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 longer acting insulin in the same sequence.

Use of NovoRapid® Penfill®

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

Read the instruction manual for the Novo Nordisk Insulin Delivery Device carefully in order to prepare your **NovoRapid® Penfill®** and operate the device correctly.

After injection, the needle should remain under the skin for at least 6 seconds. Keep the push button fully depressed until the needle has been withdrawn from the skin. This will ensure correct delivery of the dose and limit possible flow of blood or other bodily fluids into the needle or insulin cartridge.

Emergencies and overdoses

What factors may result in hypoglycemia (low blood sugar)?

If you take too much insulin, miss a meal or exercise more than usual your blood sugar may become too low (i.e. hypoglycemia). The first **symptoms of hypoglycemia** may come on

suddenly. They may include: cold sweat, cool pale skin, fatigue, drowsiness, nervousness or tremor, feelings of anxiety, unusual tiredness and weakness, confusion, difficulty concentrating, excessive hunger, changes in vision, headache, and nausea.

What to do in case of hypoglycemia?

If you experience any of the symptoms mentioned above, you should immediately take sugar, or a sweetened sugary product. Therefore, always carry a few lumps of sugar, candies, biscuits or fruit juice with you.

Your relatives, friends and close work-mates should know that you have diabetes and how they can help you if you get a severe hypoglycemic reaction. They must be aware that an unconscious person should not be given anything to eat or drink (as choking is possible), but should be turned on their side and medical assistance sought immediately. You may recover from unconsciousness more quickly if you are given an injection of the hormone glucagon by a person who has been instructed in how to use it. If glucagon is injected, you should also be given sugar, a product containing sugar or glucose by mouth as soon as you are conscious again. If you do not respond to glucagon treatment, you will have to be treated in a hospital. See your doctor if you have had repeated hypoglycemic reactions, or one leading to unconsciousness, as your insulin dose may need to be adjusted. If severe hypoglycemia is not treated, it can cause temporary or permanent brain damage or death.

What factors may result in hyperglycemia (high blood sugar)?

If you are ill with fever or if you eat much more than usual and repeatedly take less insulin than you need, your blood sugar may become unusually high (i.e. result in hyperglycemia).

The **symptoms of unusually high blood sugar levels** will appear gradually. They include: increased urination, thirst, loss of appetite, nausea, vomiting, drowsiness (fatigue), flushed dry skin, dry mouth, acetone breath.

What to do in case of hyperglycemia?

If you recognize any of the symptoms mentioned above, you should test your blood sugar level and your urine for ketones as soon as possible as the symptoms may indicate that you have a condition called ketoacidosis. If hyperglycemia is not treated it can cause diabetic coma or death. You should therefore seek medical advice immediately and possibly take some extra insulin.

What side effects may NovoRapid® cause?

NovoRapid® may cause **hypoglycemia** (low blood sugar). (See symptoms of hypoglycemia mentioned previously.) Redness, swelling or itching at the injection site (also called **local allergic reactions**) may be experienced by some people. Usually these symptoms disappear within a few weeks during continued use.

If the symptoms do not disappear, spread to other parts of your body or if you suddenly feel sick (i.e. sweats, vomits, have difficulties in breathing, have rapid heart beat, feel dizzy) you should consult your doctor immediately as these reactions may be due to **systemic allergic reactions** which are rare but may be serious.

When you first start your insulin treatment you may suffer from visual disturbances or swelling of the arms and legs, or hands and feet.

You should also tell your doctor or pharmacist if you notice any other undesirable effects which are likely to have been caused by this insulin.

Storage of NovoRapid® Vials

NovoRapid® vials which are **not being used** should be stored between 2E and 10EC preferably in a refrigerator (not too close to the freezing compartment).

NovoRapid® vials which **are being used** may be kept at room temperature (up to 30EC) for up to 4 weeks.

NovoRapid® should never be exposed to heat or direct sunlight and should never be frozen.

Keep out of reach of children.

Storage of NovoRapid® Penfill®

NovoRapid® Penfill® which is **not being used** should be stored between 2EC and 10EC preferably in a refrigerator (not too close to the freezing compartment).

NovoRapid® Penfill® that you **are using** should not be kept in a refrigerator.

NovoRapid® Penfill® can be used in a Novo Nordisk Insulin Delivery Devices or carried as a spare for up to 4 weeks.

NovoRapid® Penfill® should never be exposed to heat or direct sunlight and should never be frozen.

Keep out of reach of children.

NovoMix® 30 Patient Insert

Why have you been given NovoMix® 30?

NovoMix® 30 is an antidiabetic agent used for the treatment of diabetes mellitus as it reduces the level of sugar in the blood and urine. To control your diabetes, your doctor has prescribed injections of **NovoMix® 30**.

When injected under your skin (subcutaneously), the onset of action will occur within 10 to 20 minutes of injection, the maximum effect is between 1 and 4 hours and the effect lasts for up to 24 hours.

Availability of NovoMix® 30

NovoMix® 30 is available in the following format:

3 mL **Penfill®** cartridge, (designed for use with Novo Nordisk Insulin Delivery Devices),

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

Before you take NovoMix® 30

You should not take NovoMix® 30:

- If your blood sugar is too low (hypoglycemia). Follow the guidelines for hypoglycemia.
- If you are allergic to insulin aspart or any of the ingredients contained in **NovoMix® 30** (check with your doctor or pharmacist if you are not sure).
- **NovoMix® 30** should be given immediately before a meal. When necessary, **NovoMix® 30** may be given soon after a meal.

Dosage

Follow carefully the instructions given by your doctor concerning type of insulin, dose, and time of injection. Any change in insulin should be made cautiously and only under medical supervision. Your insulin requirements may change due to a number of factors (illness, stress, medications, changes in diet or exercise routines, etc.). Follow your doctor's instructions to allow for these changes. The following can be considered as general guidelines only and you should consult your doctor for information, which is specific to your diabetes.

Can NovoMix® 30 be taken with other medicines?

A number of drugs are known to influence insulin requirement. Therefore, if you are taking any other medication, (including over the counter medication), please consult your doctor.

What do you have to consider during pregnancy or while breastfeeding?

If you are pregnant or planning to become pregnant you should see your doctor immediately to discuss your need for and type of insulin in order to control your diabetes and avoid hyperglycemia (too high blood sugar) and hypoglycemia (too low blood sugar) as these conditions could harm your baby.

There is limited clinical experience with insulin aspart in pregnancy.

Breastfeeding while you are taking insulin does not put your baby at risk. Your insulin dosage and diet may, however, need to be adjusted.

Alcohol use

Alcohol (including beer and wine) may lead to hypoglycemia (too low blood sugar). Therefore, be careful when you drink alcohol and never drink alcohol on an empty stomach. Follow your physician's advice regarding diet and alcohol consumption.

What should be done during an illness?

Never stop taking insulin if you are ill. Your need for insulin may, however, be changed.

If you have an infection, fever or an operation you may need to have more insulin than usual.

If you suffer from diarrhea, vomiting or eat less than usual you may also need less insulin than usual.

What about travelling?

The time difference between countries may mean that you have to take your insulin and meals at different times than usual. You should therefore consult your doctor if you are planning to go abroad or travel across time zones.

Is NovoMix® 30 available in other countries?

Before you travel, check with your physician or pharmacist on availability of **NovoMix® 30** in other countries. If possible, bring enough **NovoMix® 30** with you on your trip.

How to use NovoMix® 30 Penfill®

*Before using your **NovoMix® 30 Penfill®**:*

- Do not use **NovoMix® 30 Penfill®** if it does not appear uniformly white and cloudy when rolled between your palms and turned upside down. The cartridge should not be used if clumps of material are present or if solid white particles stick to the bottom or wall of the cartridge, giving a frosted appearance.
- Before use, check that the **Penfill®** cartridge is intact (no cracks). Do not use the **Penfill®** cartridge if any damage is seen or if more of the rubber piston is visible than equal to the width of the white bar code band.

- To avoid possible transmission of disease, a **NovoMix® 30 Penfill®** cartridge must not be used by more than one person.
- Remove and dispose of the needle after each use. If the needle is not removed, temperature changes may cause liquid to leak out of the needle and the insulin concentration may change.
- Do not refill **NovoMix® 30 Penfill®**.
- Do not use **NovoMix® 30 Penfill®** in insulin pumps.
- If you switch from another insulin to **NovoMix® 30**, please consult your doctor, as your dosage may need to be adjusted.

General information on use of NovoMix® 30

- *Before injection, make sure that you have got the type and strength of insulin prescribed.*
- **NovoMix® 30** is for injection under the skin (subcutaneously). **NovoMix® 30** should not be injected intravenously.
- You will feel the effect more quickly if the insulin is injected into your abdomen. However, injections may also be given in your thigh, upper arm or buttock.
- It is recommended that you eat a meal or snack containing carbohydrate within 10 minutes of the injection.
- When necessary **NovoMix® 30** may be given soon after the meal.
- If you are treated with **NovoMix® 30 Penfill®** and another insulin in **Penfill®** cartridge, you should use two Novo Nordisk Insulin Delivery Devices, one for each type of insulin.

NovoMix® 30 Penfill®***Before insertion into a Novo Nordisk Insulin Delivery Device:***

Allow the **NovoMix® 30 Penfill®** cartridge to reach room temperature and then roll it horizontally between your palms 10 times.

Then turn the cartridge upside down 10 times so that the glass ball inside **Penfill®** moves from one end of the insulin cartridge to the other. Then rolling and turning procedure must be repeated until the liquid appears uniformly white and cloudy.

Inject immediately.

Before each injection:

If the **Penfill®** cartridge is already inside the Novo Nordisk Insulin Delivery Device turn the device upside down 10 times so that the glass ball inside **Penfill®** moves from one end of the insulin cartridge to the other. The turning procedure must be repeated until the liquid appears uniformly white and cloudy.

Injection immediately.

Injection procedure

Follow the instructions of your physician or healthcare professional on how to make injections. Read the instruction manual for the Insulin Delivery Device carefully in order to prepare your **NovoMix® 30 Penfill®** and operate the device correctly.

After injection, the needle should remain under the skin for at least 6 seconds. Keep the push button fully depressed until the needle has been withdrawn from the skin. This will ensure correct delivery of the dose and limit possible flow of blood or other body fluids into the needle or insulin cartridge.

Emergencies and overdoses**What factors may result in hypoglycemia (low blood sugar)?**

If you take too much insulin, miss a meal or exercise more than usual your blood sugar may become too low (i.e. hypoglycemia).

The first **symptoms of hypoglycemia** may come on suddenly. They may include: cold sweat, cool pale skin, fatigue, drowsiness, nervousness or tremor, feelings of anxiety, unusual tiredness and weakness, confusion, difficulty concentrating, excessive hunger, changes in vision, headache and nausea and palpitation.

What to do in case of hypoglycemia?

If you experience any of the symptoms mentioned above, you should immediately take sugar or a sugar-containing product. Therefore, always carry a few lumps of sugar, candies, biscuits or fruit juice with you.

Your relatives, friends and close work-mates should know that you have diabetes and how they can help you if you get a severe hypoglycemic reaction. They must be aware that an unconscious person should not be given anything to eat or drink (as choking is possible), but should be turned on their side and medical assistance sought immediately.

You may recover from unconsciousness more quickly if you are given an injection of the hormone glucagon by a person who has been instructed in how to use it. If glucagon is injected, you should also be given sugar, a product containing sugar or glucose by mouth as soon as you are conscious again.

If you do not respond to glucagon treatment, you will have to be treated in a hospital. See your doctor if you have had repeated hypoglycemic reactions, or one leading to unconsciousness, as your insulin dose may need to be adjusted.

If severe hypoglycemia is not treated, it can cause temporary or permanent brain damage or death.

What factors may result in hyperglycemia (high blood sugar)?

If you are ill with fever or if you eat much more than usual and repeatedly take less insulin than you need, your blood sugar may become unusually high (i.e. result in hyperglycemia).

The **symptoms of unusually high blood sugar levels** will appear gradually. They include: increased urination, thirst, loss of appetite, nausea, vomiting, drowsiness (fatigue), flushed dry skin, dry mouth, and acetone breath.

What to do in case of hyperglycemia?

If you recognize any of the symptoms mentioned above, you should test your blood sugar level and your urine for ketones as soon as possible as the symptoms may indicate that you have a condition called ketoacidosis. If hyperglycemia is not treated it can cause diabetic coma or death. You should therefore seek medical advice immediately and possibly take some extra insulin.

Possible side effects

NovoMix® 30 may cause **hypoglycemia** (low blood sugar). See symptoms of hypoglycemia mentioned previously.

Redness, swelling or itching at the injection site (also called **local allergic reactions**) may be experienced by some people. Usually these symptoms disappear within a few weeks during continued use.

If the symptoms do not disappear, spread to other parts of your body or if you suddenly feel sick (i.e. sweat, vomit, have difficulties in breathing, have rapid heart beat, feel dizzy) you should

consult your doctor immediately as these reactions may be due to **systemic allergic reactions** which are rare but may be serious.

When you first start your insulin treatment you may suffer from visual disturbances or swelling of the extremities.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Storing NovoMix® 30 Penfill®

Store **NovoMix® 30 Penfill®** which you are **not using** at 2°C - 10°C preferably in a refrigerator (not too near the freezer compartment). **NovoMix® 30** should never be exposed to heat or direct sunlight and should never be frozen.

NovoMix® 30 Penfill® that you **are using** must not be kept in a refrigerator.

NovoMix® 30 Penfill® can be used or carried as a spare for up to 4 weeks (not above 30°C).

Keep out of the reach of children.

Do not use after the expiry date stated on the label and carton.

Do not use **NovoMix® 30 Penfill®** if it does not appear uniformly white and cloudy after shaking.

This summary does not contain all the known information about NovoMix® 30. Talk to your doctor if you have any questions.

PHARMACOLOGY

Insulin aspart is an analogue of human insulin, in which the amino acid, proline, in position 28, has been replaced by aspartic acid. This modification was designed to target the part of the molecule responsible for self association. Due to charge repulsion, insulin aspart has a reduced tendency to self associate. This causes insulin aspart to be absorbed more rapidly, resulting in faster action. Insulin aspart is designed to be similar to human insulin in all other aspects.

The biological activity of insulin aspart has been evaluated *in vivo* in mouse, rabbit and pig and, *in vitro* in a free fat cell assay.

In a comparison of hypoglycemic activity of insulin aspart and human insulin in the diabetic ob/ob mouse, insulin aspart reduced moderate hyperglycemia to a similar extent as an equimolar dose of human insulin.

The molar potency of insulin aspart was compared to that of a human insulin standard using the mouse blood glucose assay according to Ph. Eur. and the rabbit blood sugar method according to USP. Using the mouse blood glucose assay, the potency of three different batches of insulin aspart was determined to be 104.4% (95% confidence limits: 96.1-113.4%), 105.4% (93.8-118.3%), and 104.8% (94.3-116.5%) relative to the first international human insulin standard. Thus, the potency of insulin aspart is not significantly different from that of human insulin in the mouse blood glucose assay. The molar potency of insulin aspart is defined as 1U = 6 nmol. Potency estimates for insulin aspart determined by the rabbit blood sugar assay were equivalent to those determined by the mouse blood glucose assay.

Studies in pigs show that equimolar amounts of insulin aspart and human insulin have similar effects on blood glucose after i.v. administration, and that insulin aspart has a faster action than human insulin after s.c. administration.

In the free fat cell bioassay, the potency of insulin aspart was determined to be 102.7 % (95% confidence limits: 99.6-105.8%) relative to a human insulin standard. Thus, the potency of insulin aspart is not significantly different from that of human insulin in free fat cells.

The performed bioassays show that the potency of insulin aspart is equal to that of human insulin. A competitive ligand binding analysis using confluent HepG2 cells explored the relative binding affinities of insulin aspart and human insulin for the insulin receptor. There was no difference in their affinity. The affinity of insulin aspart for the insulin receptor was determined to be 92.2% (95% confidence limits 82.0-103.7%) of that of human insulin using HepG2 cells and to 92% of that of human insulin using solubilised receptors.

A very low affinity for the human IGF-1 receptor on HepG2 cells was also demonstrated; 68.8% compared to human insulin and about 1/1000th of the binding affinity of IGF-1 itself.

These studies show that insulin aspart has almost identical biological properties to human insulin, including affinity for the specific insulin receptor, and similar on- and off-rates at that receptor.

Cardiovascular studies in anaesthetized rats and pigs plus a range of standard behavioural and organ function test and interaction studies have been conducted. Dose levels used in rodents were up to 100 times higher than the expected human therapeutic dose of 1 U/kg. In cats and pigs the high dose was 4 times higher than the expected human therapeutic dose due to the higher sensitivity of these species.

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

Test	Insulin Aspart/ Human Insulin(HI)	Results
Pro-convulsant activity, mice	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No effects
Analgesic effect on acetic acid induced writhing	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No effects
Effects on body temperature	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No effects
Isolated guinea-pig ileum	3.6, 36 or 360 mU/mL HI: 360 mIU/mL	No effects
Autonomic nervous system in anaesthetised cat	0.4, 1.0 and 4.0 U/kg IV, HI: 0.4, 1.0 and 4.0 IU/kg IV	No difference from human insulin was observed
Cardiovascular and Respiratory Systems in anaesthetised rat	1,10 and 100 U/kg IV, HI: 1,10 and 100 IU/kg IV	No effects
Cardiovascular and Respiratory Systems in anaesthetised pig	0.4, 1.0 and 4.0 U/kg IV. HI: 0.4, 1.0 and 4.0 IU/kg IV	No difference from human insulin was observed
Gastrointestinal Motility in Mice	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No effects
Renal Function in Rats	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No effects in general

TOXICOLOGY

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.

Acute Toxicity:

Results of Acute Toxicity Studies with Insulin aspart

Species, Strain, Route	(M+F) Animals per group	Doses U/kg	Results
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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 hypoglycaemia 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:

Results of long-term toxicity studies with insulin aspart

Species	Strain	Number of groups and size	Dosing Method	Duration (Weeks)	Dose level (U/kg/day)	Results
Rat	Sprague-Dawley	5 Groups 10M, 10F/group, main 9M, 9F/group, satellites 5M, 5F in groups 1, 4 & 5 reversibility assessment	SC	4 weeks + 4 week recovery in groups 1, 4 & 5	0, 5, 25, 100 + 100	Hypoglycemia, increased food consumption and weight gain. No unexpected observations.
Rat	Sprague-Dawley	4 Groups 10M, 10F	SC	4 weeks	0, 12.5, 50, 200	Hypoglycemia. No unexpected observations.
Rat	Mol: WIST	4 Groups 15M, 15F	SC	13 weeks	0, 12.5, 50, 200	Hypoglycemia, increased weight gain. No unexpected observations.
Rat	Sprague-Dawley	4 Groups 32M, 32F Satellites included	SC	52 weeks	Top dose levels 100 bid for 24 weeks, 50 bid weeks 25-26, 100 od weeks	Hypoglycemia, increased food and water consumption and weight gain.

Species	Strain	Number of groups and size	Dosing Method	Duration (Weeks)	Dose level (U/kg/day)	Results
					27-37, 75 od from week 38-52. Lower dose levels 5 and 25U/kg/bid for 26 weeks 10 and 50 od for 27- 52 weeks. Controls.	Excess of mammary tumours in high dose females.
Rat	Sprague- Dawley	4 Groups 20F	SC	52 weeks	200 per drug substance. Insulin aspart, human insulin, control.	Mammary tumour-incidence higher in insulin aspart group equal to human insulin both being higher than controls.
Dog	Beagle	4 groups 3M, 3F/group, main 1M, 1F in groups 1 & 4 reversibility assessment	SC	4weeks (+ 4 week recovery in groups 1 & 4)	0, 0.25, 0.5 , 1.0 bid	Hypoglycemia. No unexpected observations.
Dog	Beagle	3 Groups 4M, 4F	SC	13 weeks	0,1, 4	Hypoglycemia. No unexpected observations.
Dog	Beagle	4 Groups 4M, 4F	SC	52 weeks	0, 0.25, 0.5, 1.0 bid for 28 weeks same daily dose od from week 29-52. HI- 1.0 bid 28 weeks 2.0 od from 29-52	Hypoglycemia. No unexpected observations.

Carcinogenicity:

Carcinogenicity trials have not been performed with **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.

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