PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Kirsty®

Insulin Aspart Injection

100 Units / mL, Subcutaneous

Anti-diabetic Agent

ATC code: A10AB05

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85 Advance Road
Etobicoke, Ontario
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RECENT MAJOR LABEL CHANGES

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Kirsty® (Insulin Aspart) is a biosimilar biologic drug (biosimilar) to NovoRapid.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Indications have been granted on the basis of similarity between Kirsty (Insulin Aspart) and the reference biologic drug NovoRapid

Kirsty® (insulin aspart) is indicated for:

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

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

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

1.1 Pediatrics

Pediatrics (2 – 17 years of age):
Evidence from clinical studies and experience suggests that use in the pediatric population is not associated with any differences in safety or effectiveness. Please see 11 ACTION AND CLINICAL PHARMACOLOGY.

1.2 Geriatrics

Geriatrics (> 65 years of age):
There was no clinically relevant difference in the pharmacokinetics and pharmacodynamics of insulin aspart between elderly and younger subjects. Please see 8 WARNINGS AND PRECAUTIONS and 11 ACTION AND CLINICAL PHARMACOLOGY.

2 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 6 DOSAGE FORMS, STRENGTH, COMPOSITION and PACKAGING of the product monograph.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Hypoglycemia is the most common adverse effect of insulin products. As with all insulin products the timing of hypoglycemia may differ. Glucose monitoring shall be performed for all patients with diabetes mellitus treated with insulins. (see HYPOGLYCEMIA, HYPERGLYCEMIA AND OVERDOSAGE).
- Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma or even death. (see ENDOCRINE AND METABOLISM – HYPOGLYCEMIA).
- Any transfer of insulin products should be made cautiously and only under medical supervision. (see 8 WARNINGS AND PRECAUTIONS).
- Some insulin products are short-acting insulin and are known for their rapid onset and short duration of action. The injection of such insulin products should immediately be followed by a meal (within 5-10 minutes or given immediately after the meal. (see 4 DOSAGE AND ADMINISTRATION).
- Short-acting insulin should be combined with a longer-acting insulin or insulin infusion pump therapy to maintain adequate glucose control. (see 4 DOSAGE AND ADMINISTRATION).
- Insulin products shall not be mixed with any other insulin unless clearly indicated and done under medical supervision. (see 8 WARNINGS AND PRECAUTIONS).
- Insulin products shall not be used if it is not water-clear and colourless or if it has formed a deposit of solid particles on the wall of the vial or cartridge. (see 4 DOSAGE AND ADMINISTRATION).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Patients being initiated on insulin can be started on Kirsty® in the same manner as they would be on animal-source or human insulin.
- Changes for patients being transferred from other insulin to Kirsty® should be made as directed by a physician.

4.2 Recommended Dose and Dosage Adjustment

Due to its faster onset of action, Kirsty® 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, Kirsty® may be given immediately after the meal.

Dosage of Kirsty® 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 Kirsty® and the remainder provided by an intermediate-acting or long-acting insulin.

The dosing of Kirsty® should be regularly adjusted according to blood glucose

measurements. Adjustment dosage may also be necessary if patients undertake increased physical activity or change their usual diet. Exercise taken immediately after a meal may increase the risk of hypoglycemia.

4.4 Administration

Kirsty® (insulin aspart) is administered subcutaneously by injection in the abdominal wall, the thigh, the upper arm, the deltoid region or the gluteal region. Injection sites should be rotated within the same region from one injection to the next so that the same site is not used more than approximately once a month in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see sections 8 WARNINGS and PRECAUTIONS and 9 ADVERSE REACTIONS). Insulin aspart 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 Kirsty® if it has become viscous (thickened) or cloudy; use it only if it is water-clear and colourless. Kirsty® should not be used after its expiration date.

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.

Kirsty® (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 Kirsty® by CSII must have an alternate insulin delivery device available in case of pump system failure.

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

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

5 OVERDOSAGE

Excess insulin administration may cause hypoglycemia and, particularly when given intravenously, hypokalemia. Hypoglycemia may occur as a result of an excessive

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

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

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

For management of a suspected drug overdose, contact your regional poison control centre immediately.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 1: – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous	Solution for injection / 100 Units / mL	Disodium hydrogen phosphate dihydrate; glycerol; metacresol; phenol; sodium chloride; water for injection and zinc chloride. Hydrochloric acid and sodium hydroxide are used for pH adjustment.

Kirsty® is available in 10 mL multiple-dose vial and in 3 mL disposable pre-filled pen.

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 pre-filled pen include 1 x 3 mL pre-filled pen and 5 x 3 mL pre-filled pens.

7 DESCRIPTION

Kirsty® (insulin aspart) is a rapid-acting human insulin analog, produced by recombinant DNA technology utilizing Pichia pastoris (yeast) cells, that rapidly lowers blood glucose. Kirsty® 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 Kirsty® reduces the tendency to form hexamers as observed with regular human insulin. Kirsty® is therefore more rapidly absorbed from the subcutaneous layer compared to regular human insulin.

8 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX at the beginning of Part I: Health Professional Information.

General

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

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

Thiazolidinediones (TZDs), alone or in combination with other anti-diabetic agents (including insulin), can cause heart failure and oedema. The combination of insulin with a TZD is not indicated for the treatment of type 2 diabetes mellitus. Please refer to the respective TZD product monograph, (see WARNINGS AND PRECAUTIONS), information when the use of these drugs in combination with any insulin, including insulin aspart, is contemplated.

Kirsty® pre-filled pen should never be shared between patients, even if the needle is changed. Sharing poses a risk for transmission of blood-borne pathogens.

Avoidance of accidental mix-ups/medication errors

Patients must be instructed to always check the insulin label before each injection to

avoid accidental mix-ups between insulin aspart and other insulin products.

Carcinogenesis and Mutagenesis
See 18 Non-Clinical Toxicology.

Driving and Operating Machinery
Caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

Endocrine and Metabolism

Hypoglycemia
As with other insulins, hypoglycemia is the most common adverse effect of insulin therapy, including Kirsty. Such reactions following treatment with insulin aspart are mostly mild and easily managed. While the frequency of hypoglycemia observed in clinical trials is similar to that observed with regular human insulin, clinical trials in patients with type 1 diabetes have demonstrated a reduced risk of nocturnal hypoglycemia with insulin aspart compared with soluble human insulin. The risk of daytime hypoglycemia was not significantly increased.

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of Kirsty. 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 betablockers, or intensified diabetes control.

Patients, whose blood glucose control is greatly improved, e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycemia, and should be advised accordingly. Usual warning symptoms may disappear in patients with long-standing diabetes. Hypoglycemia may occur if the insulin dose is too high in relation to the insulin requirement. (see 9 ADVERSE REACTIONS, Hypoglycemia and 5 OVERDOSAGE)

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

Stress or concomitant illness, especially infectious and febrile conditions may change insulin requirements. In these instances, patients should contact their physician and carefully control their blood glucose. Concomitant diseases in the kidney, liver or affecting the adrenal, pituitary or thyroid gland can require changes in the insulin dose.

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

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

The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycemia while driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycemia or have frequent episodes of hypoglycemia. The advisability of driving should be considered in these circumstances.

Glucose monitoring is recommended for all patients with diabetes.

Hyperglycemia

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

Hypokalemia

All insulin products, including Kirsty®, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia that, if left untreated, may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia [e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations, patients receiving intravenously administered insulin, or patients losing potassium through other means (e.g., diarrhea)]. (see 9 ADVERSE REACTIONS).

Hepatic/Biliary/Pancreas

The pharmacokinetics of insulin aspart 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, Kirsty®

requirement may need to be adjusted in patients with hepatic impairment.

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

Immune

Local allergic reaction

As with any insulin therapy, injection site reactions may occur and include pain, redness, itching, hives, swelling, bruising and inflammation. Continuous rotation of the injection site within a given area reduces the risk of developing these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of Kirsty®. Localized reactions and generalized myalgias have been reported with injected metacresol, which is an excipient in insulin aspart.

Systemic Allergic Reaction

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

Antibody production

Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper or hypoglycemia.

In the clinical development program, insulin aspart-specific, regular human insulin-specific and cross reactive antibodies were analyzed. Antibody production was monitored in 665 patients for 12 months. After a transient statistically significant increase in cross-reacting antibodies from baseline to 3 months for insulin aspart compared to human insulin, cross-reacting antibody levels returned to baseline levels in the insulin aspart 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 insulin aspart (n=157) during pregnancy in patients with type 1 diabetes, mean levels of antibodies specific to insulin aspart were low (<3%). Variability between patients was up to 14% for insulin aspart. The majority of antibodies were cross-reacting. There was no observable increase in antibodies with insulin aspart treatment from baseline to the end of the third trimester.

Similar observations were found in cord blood. Mean levels of antibodies specific to insulin aspart were low (<1%). The majority of insulin antibodies were cross-reacting, and variability between patients was up to 17% for insulin aspart 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 insulin aspart specific antibodies.

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

See also 8 WARNING AND PRECAUTIONS, Sexual Function/Reproduction and Special Populations, Pregnant Women, 9 ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, Pregnancy clinical trials; and Part II, SCIENTIFIC INFORMATION, 17 CLINICAL TRIALS, type 1 diabetes.

Mixing of Insulins

Mixing of an insulin formulation with another insulin formulation may change the pharmacokinetic and/or pharmacodynamic profile of action of the combined mixture in an unpredictable matter.

Monitoring and Laboratory Tests

As with all insulin therapy, the need for regular blood glucose self-monitoring should be considered when using Kirsty® to obtain optimal glycemic control. Periodic measurement of glycated hemoglobin is recommended for the monitoring of long-term glycemic control. If a patient is pregnant, careful monitoring of the patient is required throughout pregnancy. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.

Renal

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

variable of insulin aspart. As with other insulins, insulin aspart requirement may be reduced in patients with renal impairment. Insulin aspart requirement may need to be adjusted in patients with severe renal impairment.

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

Sexual Health

Reproduction

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

Skin and subcutaneous tissue disorders

Subcutaneous administration of insulin products, including Kirsty can result in lipoatrophy (thinning of adipose tissue) or lipohypertrophy (thickening of adipose tissue) or localized cutaneous amyloidosis (skin lumps) which may affect insulin absorption.

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. Patients should be advised to consult their health professional if they notice any of these conditions and before changing the injection site. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site from an affected to an unaffected area, and dose adjustment of antidiabetic medications may be considered.

8.1 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.

8.2 Special Populations

8.2.1 Pregnant Women

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

In a clinical trial of 157 pregnant women with type 1 diabetes treated with insulin aspart 10 congenital malformations were reported in 9 (5.7%) patients treated with insulin aspart. Cardiac anomalies were reported (n=7), mainly septal defects (n=4). Additional reports in offspring of patients treated with insulin aspart were one each of central nervous system anomaly, ankyloglossia and fetal disorders.

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

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

See also 8 WARNINGS AND PRECAUTIONS, Immune and Special Populations, Pregnant Women; 9 ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, Pregnancy clinical trials; and Part II, SCIENTIFIC INFORMATION, 17 CLINICAL TRIALS, type 1 diabetes.

Insulin aspart 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 insulin aspart. Two-thirds (n=113) of the enrolled patients were already pregnant when they entered the study. Because only one third (n=44) of the patients were enrolled before conception, the sample size was not large enough to evaluate the risk of congenital malformations. A1C was evaluated during the study as well as the

incidence of hypoglycemia. (see also, 9.2 Clinical Trial Adverse Drug Reactions, Pregnancy clinical trials and Part II, SCIENTIFIC INFORMATION, 17 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 insulin aspart.

8.2.2 Breast-feeding

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

8.2.3 Pediatrics

Pediatrics (2-17 years of age): The pharmacokinetic properties of 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 insulin aspart and regular human insulin correlated well with those in healthy adult subjects and type 1 diabetic adults.

The efficacy and safety of insulin aspart 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. Insulin aspart, 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 ± 0.23% vs 7.56 ± 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 insulin aspart in adults with type 1 diabetes. In addition, as compared to regular human insulin, insulin aspart 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 insulin aspart were compared to insulin lispro and regular human insulin in a 24-week, randomized, open label study in 378 children (6-18 years of age) with type 1 diabetes. NPH insulin was administered as basal insulin. Baseline means A1C values for insulin aspart, lispro and regular human insulin were 8.3 ± 1.2%, 8.4% ± 1.2% and 8.3 ± 1.2%, respectively. At the

end of the study, patients had mean A1C values of 8.4 ± 1.4%, 8.2 ± 1.2% and 8.3 ± 1.4%, respectively. The changes from baseline were not significantly different among the groups. Insulin aspart demonstrated similar, postprandial, blood glucose levels as lispro. The blood glucose levels after lunch and dinner decreased significantly with insulin aspart than with regular human insulin (lunch: 10.2 ± 4.5 mmol/L vs. 11.2 ± 4.7mmol/L, respectively; p=0.009; dinner: 10.5 ± 4.4 mmol/Lvs.11.6 ± 4.8mmol/L, respectively; p=0.003. Furthermore, insulin aspart did not increase the risk of hypoglycemia and had a safety profile comparable to both regular human insulin and lispro.

8.2.4 Geriatrics

PK/PD study comparing insulin aspart with soluble human insulin was performed in 19 elderly patients with type 2 diabetes. The relative differences in the pharmacodynamic properties between insulin aspart and human insulin in elderly were consistent with those seen in healthy subjects and in younger patients with diabetes. However, careful glucose monitoring and individual dose adjustments of insulin, including insulin aspart, may be necessary in elderly patients. (see 11 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 insulin aspart for up to 6 months. No differences in dose, efficacy or adverse events were observed between these patients and younger population.

8.2.5 Others

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

8.2.6 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.

8.2.7 Obesity

The influence of obesity and/or subcutaneous fat thickness on the pharmacokinetics and glucodynamics of insulin aspart has not been studied. Patients with a body mass index (BMI) up to 40kg/m^2 were treated with insulin aspart. No difference was observed in efficacy and safety compared to leaner patients.

8.2.8 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.

8.2.9 Smoking

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

9 ADVERSE REACTIONS

The adverse drug reaction profiles reported in clinical studies that compared Kirsty to the reference biologic drug were comparable. The description of adverse reactions in this section is based on clinical experience with the reference biologic drug.

9.1 Adverse Reaction Overview

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

9.2 Clinical Trial Adverse 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 reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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

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

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

Symptoms of generalised hypersensitivity may include generalised skin rash, itching, sweating gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation and reduction in blood pressure. Generalised hypersensitivity reactions are potentially life threatening.

Nervous system disorders

Rare (>1/10,000, <1/1000): Peripheral neuropathy

Fast improvement in blood glucose control may be associated with a condition termed acute painful neuropathy, which is usually reversible.

Eye disorders

Uncommon (>1/1000, <1/100): Refraction disorder

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

Uncommon (>1/1000, <1/100): Diabetic retinopathy

Long-term improved glycemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders

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

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

Uncommon (>1/1000, <1/100): Local hypersensitivity

Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.

General disorders and administration site conditions

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

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

Pregnancy Clinical Trials

In a clinical trial comparing safety and efficacy of insulin aspart to insulin human in the treatment of pregnant women with type 1 diabetes (322 exposed pregnancies 157 to insulin aspart 165 to human insulin) the adverse event profiles were similar in

patients receiving insulin aspart and those receiving regular human insulin with respect to incidence and severity. Most adverse events were mild or moderate in severity. With the exception of obstetric complications, the adverse event profile was similar in patients during pregnancy and outside pregnancy. There were no differences in the incidence of obstetric complications between treatment groups.

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

Serious adverse events with possible or probable relation to trial drug were reported with insulin aspart 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 insulin aspart: spontaneous abortion, missed abortion and caesarean section. (see also WARNINGS AND PRECAUTIONS, Immune, and Sexual Functions/reproduction and Special populations; Pregnant Women; and Part II. SCIENTIFIC INFORMATION, 17 CLINICAL TRIALS, type 1 diabetes)

9.3 Less Common Clinical Trial Adverse Reactions (<1%)

In addition, the following adverse events were reported at an incidence of <1% for insulin aspart 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 (insulin aspart 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 insulin aspart 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 insulin aspart 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 insulin aspart 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.

9.4 Post-Market Adverse Reactions

Adverse Drug Event Overview for a Post-Marketing CSII Trial
A 4 month post-marketing study in 511 patients with type 1 and insulin-requiring type 2 diabetes mellitus was conducted as a preference trial to assess the treatment satisfaction of insulin aspart 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 ≥ 1% was upper respiratory tract infection (incidence of 1.3% in the insulin aspart 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 insulin aspart 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 insulin aspart in Study 2190:

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

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

10 DRUG INTERACTIONS

10.1 Overview

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

10.2 Drug-Drug Interactions

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

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

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

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

Octreotide/lanreotide may either increase or decrease insulin requirements.

To avoid the risk of developing new or worsening heart failure, the use of TZDs in combination therapy with Kirsty is not indicated. (see 8 WARNINGS AND PRECAUTIONS)

10.3 Drug-Food Interactions

Please refer to 11 ACTION AND CLINICAL PHARMACOLOGY, Mechanism of Action and 4 DOSAGE AND ADMINISTRATION for interactions with food and timing

of food consumption, respectively.

10.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

10.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10.6 Drug-Lifestyle Interactions

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

The influence of obesity and/or subcutaneous fat thickness on the pharmacokinetics and glucodynamics of insulin aspart has not been studied. Patients with a body mass index (BMI) up to 40kg/m^2 were treated with insulin aspart. No difference was observed in efficacy and safety compared to leaner patients.

Patients should be informed about potential advantages and disadvantages of 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 Kirsty to obtain optimal glycemic control.

Alcohol may intensify or reduce the hypoglycemic effect of insulin.

11 ACTION AND CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

The primary activity of insulin aspart is the regulation of glucose metabolism. Insulins, including insulin aspart, 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 insulin aspart is equipotent to regular human insulin on a molar basis.

Insulin aspart 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 insulin aspart more closely mimics normal physiological postprandial insulin release than regular human insulin used as replacement therapy. This effect leads to reduced postprandial variability in blood glucose concentration.

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

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

11.2 Pharmacodynamics

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 3-5 hours.

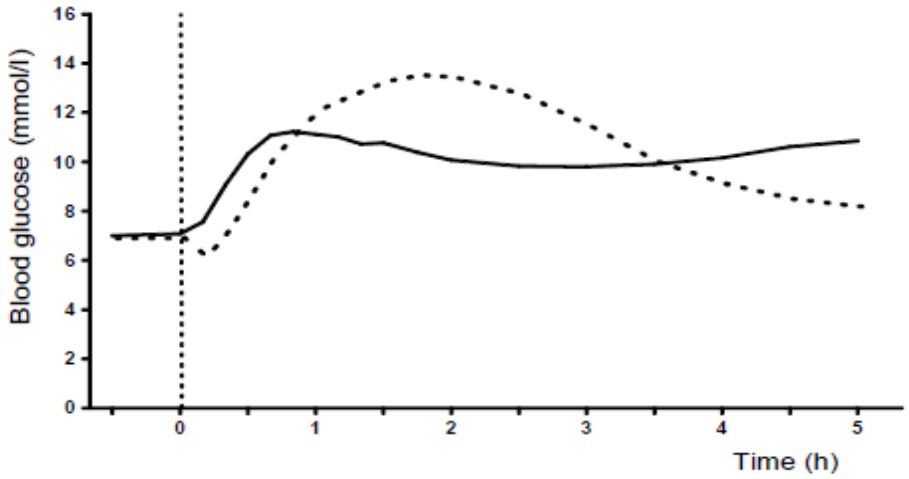


Fig. 1: Mean blood glucose levels following a single pre-meal subcutaneous dose (0.15U/kg) of insulin aspart injected immediately before a meal (solid line) or regular human insulin administered 30 minutes before a meal (hatched line) in 22 patients with type 1 diabetes.

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

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

Children and adolescents (2-17 years):
When given to children insulin aspart showed similar long-term glucose control compared to soluble human insulin.

11.3 Pharmacokinetics

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

Insulin aspart is therefore more rapidly absorbed from the subcutaneous layer compared to soluble human insulin.

The time to maximum concentration is on average, half of that for soluble human insulin. A mean maximum plasma concentration of 492 ± 256 pmol/l was reached 40 (interquartile range: 30-40) minutes after a subcutaneous dose of 0.15 U/kg bodyweight in type 1 diabetic patients. The insulin concentrations returned to baseline about 4 to 6 hours after dose. The absorption rate was somewhat slower in type 2 diabetic patients, resulting in a lower C_{max} (352±240 pmol/l) and later t_{max} [60 (interquartile range: 50-90) minutes]. The intra-individual variability in time to maximum concentration is significantly less for insulin aspart than for soluble human insulin, where the intra-individual variability in C_{max} for insulin aspart is larger.

Reduced renal or hepatic function does not alter the pharmacokinetics of insulin aspart.

Absorption: 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 insulin aspart 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, insulin aspart consistently reached maximum serum concentration at least twice as fast as regular human insulin. The average median time to maximum serum concentration was 40-50 minutes for insulin aspart versus 80-120 minutes for regular human insulin. The intra-individual variability in time to maximum concentration was significantly less for insulin aspart than for regular human insulin.

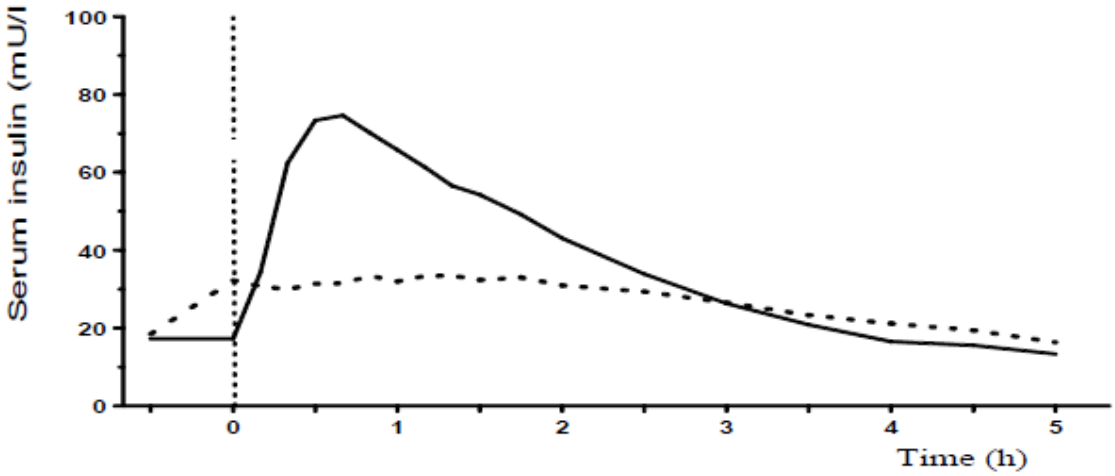


Fig 2: Mean serum insulin concentration following a single pre-meal subcutaneous

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

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

In healthy subjects, the pharmacokinetic differences between insulin aspart 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, insulin aspart 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 insulin aspart is 3-5 hours compared to 5-8 hours for regular human insulin. In this trial, patients were clamped from the evening before the trial product administration in order to obtain a blood glucose concentration of 5-8 mmol/l.

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

The extent of absorption (AUC) and t_{max}(ins) for insulin aspart were found to be independent of injection site when insulin aspart 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 insulin aspart, significantly improved long-term metabolic control was obtained compared to regular human insulin after 6 months treatment, the values being 7.78±0.03% for insulin aspart and 7.93±0.05% ($p < 0.01$) for regular human insulin in one trial and correspondingly 7.88±0.03% and 8.00±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 insulin aspart in a meal-related regimen for 6 months, the pharmacodynamic properties of insulin aspart 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 insulin aspart 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 insulin aspart is reflected in the return of insulin aspart concentrations to pre-dosing levels within 4 hours after dosing.

Special Populations and Conditions

Pediatrics: The pharmacokinetic properties of 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 insulin aspart 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 insulin aspart.

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

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

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 insulin aspart pharmacokinetic parameter. Careful glucose monitoring and dose adjustments of insulin, including insulin aspart, may be necessary in patients with hepatic dysfunction. (see 8 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 insulin aspart was administered in a study of 18 patients with creatinine clearance values ranging from normal to <30 mL/min and not requiring hemodialysis. No apparent effect of creatinine clearance values on AUC and C_{max} of insulin aspart was found. However, only 2 patients with severe renal impairment were studied (<30 mL/min). Careful glucose monitoring and dose adjustments of insulin, including insulin aspart on AUC and C_{max} of insulin aspart was found. However, only 2 patients with severe renal impairment were studied (<30 mL/min). Careful glucose monitoring and dose adjustments of insulin, including insulin aspart, may be necessary in patients with renal dysfunction. (see 8 WARNINGS AND PRECAUTIONS, Renal)

12 STORAGE, STABILITY AND DISPOSAL

Keep out of the reach and sight of children. Keep Kirsty® protected from heat or light.

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

10 mL vial:

Before opening: Store in a refrigerator at 2°C to 8°C, away from the cooling element. Do not freeze. Protect from light.

During use or when carried as a spare: Store below 30°C. The product may be stored for a maximum of 4 weeks. Do not refrigerate or freeze

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

Pre-filled pen:

Before opening: Kirsty® pre-filled pen that is not being used is to be stored in the refrigerator at 2°C to 8°C, away from the cooling element. Do not freeze.

During use or when carried as a spare: You can carry your Kirsty® pre-filled pen with you and keep it at a temperature below 30°C or in a refrigerator (2˚C to 8˚C) for up to 4 weeks. If refrigerated, keep away from the cooling element. Do not freeze.

The Kirsty® pre-filled pen you are using should be thrown away after 4 weeks, even if it still has insulin left in it. Do not use this medication after the expiration date stated on the label.

13 SPECIAL HANDLING INSTRUCTIONS

Kirsty® pre-filled pen should never be shared between patients, even if the needle is changed. The cartridge must not be refilled. The patient should be advised to discard the needle after each injection.

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

Kirsty® which has been frozen must not be used.

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

PART II: SCIENTIFIC INFORMATION

14 PHARMACEUTICAL INFORMATION

Drug Substance

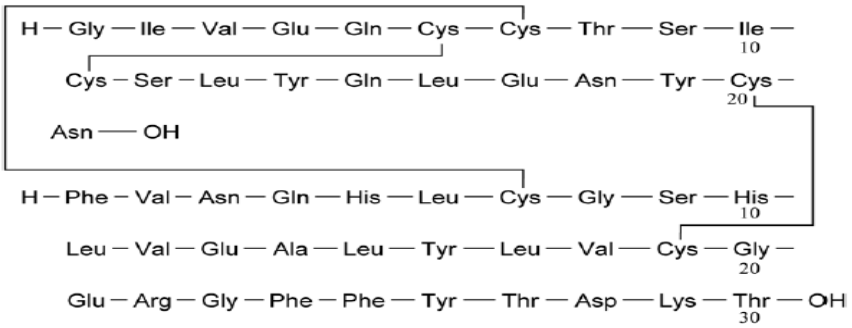
Proper name: Insulin Aspart

Chemical name: 28^{B}-L-Aspartic acid-insulin (human) analogue

Molecular formula and molecular mass: $C_{256}H_{381}N_{65}O_{79}S_6$ and 5825.56 Da

Insulin aspart is a 2-chain peptide containing 51 amino acids. The A-chain is composed of 21 amino acids, and the B-chain is composed of 30 amino acids. It is identical in primary structure to human insulin, except that it has an aspartic acid instead of proline at position 28 of the B-chain. As in human insulin, insulin aspart has 2 interchain (A7:B7 & A20:B19) and 1 intrachain (A6:A11) disulphide bond.

Structural formula: Insulin Aspart



Physicochemical properties:

Description: White, or almost white powder

Solubilities:

Practically insoluble in Ethanol (96%), in Methanol and in aqueous solvent at pH around 5.1. Soluble in aqueous solutions below pH 3.5 or above pH 6.5, the solubility is greater than 25 mg/ml.

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

Product Characteristics

The manufacture of the drug substance consists of the following three major steps: fermentation, recovery, and purification. During the fermentation, the insulin aspart precursor protein is released into the fermentation medium. After harvesting, the precursor is isolated and converted to the active molecule of insulin aspart and purified with different chromatographic steps during the downstream process stages.

15 COMPARATIVE CLINICAL TRIALS

15.1 Comparative Trial Design and Study Demographics

Clinical studies conducted to support similarity between Kirsty and the reference biologic drug included:

- MYL-1601D-1001, a randomized study performed in healthy participants to demonstrate similarity in pharmacokinetic (PK) exposure and pharmacodynamic (PD) activity between Kirsty and NovoRapid/NovoLog
- MYL-1601D-3001, a randomized, open-label, parallel-group clinical study comparing the safety and efficacy of Kirsty and NovoLog in Type 1 Diabetes Mellitus patients

An overview of the study design(s) and demographic characteristics of patients enrolled in each clinical study are presented in Table 2.

Table 2 - Summary of Trial Design and Patient Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age ± SD (Range)	Sex
MYL-1601D-1001	Randomized, double-blind, three-treatment, three-period, crossover PK/PD study	Test Product: MYL-1601D Reference products: NovoRapid® (insulin aspart), NovoLog® (insulin aspart) All IMPs were administered as 0.2 U/kg b.w. from 10 mL - 100 U/mL vial -single, s.c. dose	Healthy participants 71 -dosed 66 -completed	37.2 ± 11.4 (21 to 61)	62 male 9 female
MYL-1601D-3001	Randomized, multicenter, open-label, parallel-group	Test product: MYL-1601D. Reference Products: NovoLog®. During the Run-in period, all subjects were received FlexPen® NovoLog® ,100 U/mL until randomization.	Type 1 Diabetes Mellitus Patients 528 randomized,	44.3 ± 13.61 (18 to 65)	261 male 217 female

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age ± SD (Range)	Sex
	clinical study comparing the safety and efficacy of MYL-1601D with NovoLog®	During the Treatment period, all patients will receive one of the following treatments: MYL-1601D or FlexPen® NovoLog® taken at mealtime. Both investigational products were provided in a pre-filled disposable pen with a 3-mL cartridge. In addition, all subjects received once daily Lantus® SoloSTAR® (insulin glargine injection, 100 U/mL), manufactured by Sanofi-Aventis. During the treatment period, dose titration was kept to a minimum. All IMPs were admintered via subcutaneous injection.	485 completed treatment		

15.2 Comparative Study Results

15.2.1 Comparative Bioavailability Studies

15.2.1.1 Pharmacokinetics

Comparative Pharmacokinetics Data from Study MYL-1601D-1001

Insulin Aspart (1 x 0.2 U/kg b.w.) From measured data Geometric Mean Arithmetic Mean (CV %)

Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
$AUC_{(0\text{-}12hr)}$ (pg*hr/mL)	8065 8188 (18)	7933 8015 (15)	101.8	100.0 – 103.7
AUC_I (pg*hr/mL)	8167 8288 (18)	8041 8124 (15)	101.7	100.0 – 103.5
C_{MAX} (pg/mL)	3049 3178 (30)	2897 2972 (23)	105.7	101.1 – 110.6
T_{MAX}[3] (h)	1.03 (42.78)	1.10 (48.64)		
$T_{½}$[3] (h)	0.88 (29.12)	0.89 (30.14)		

[1] MYL-1601D (Kirsty® - Mylan Insulin Aspart Solution for Injection, 100 U/mL)
[2] NovoRapid®, 100U/mL, NovoNordisk A/S (purchased from Germany)
[3]Expressed as the arithmetic mean (CV%) only.
N=67 for each Test and Reference dosing period.
The primary PK endpoints AUC and C_{max} were analyzed using logarithm-transformed data. The ANOVA were based on a general linear model (sas proc GLM).

15.2.1.2 Pharmacodynamics

Comparative Pharmacodynamics Data from Study MYL-1601D-1001

Blood Glucose From measured data Geometric Mean Arithmetic Mean (CV %)

Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	95% Confidence Interval
$AUC_{(GIR\ 0\text{-}last)}$ (mg/kg)	2655 2773 (29)	2736 2869 (31)	96.4	91.2 – 102.0
GIR_{MAX} (mg/kg/min)	9.33 9.85 (32)	9.77 10.24 (30)	95.1	89.4 – 101.2
T_{MAX}[3] (h)	2.74 (39)	2.90 (32)		

[1] MYL-1601D (Kirsty® - Mylan Insulin Aspart Solution for Injection, 100 U/mL)
[2] NovoRapid®, 100U/mL, NovoNordisk A/S (purchased from Germany)
[3]Expressed as the arithmetic mean (CV%) only.
N=67 for each Test and Reference dosing period.
The primary PD endpoints $AUC_{(GIR\ 0\text{-}last)}$ and GIR_{max} were analyzed using logarithm-transformed data. The ANOVA were based on a general linear model (sas proc GLM).

Comparative Safety and Efficacy

15.2.1.1 Safety

The types, frequency and severity of adverse events were comparable between the biosimilar and the reference biologic drug.

Study MYL-1601D-3001 was a multicenter, open-label, randomized, parallel-group Phase 3 study in subjects with type 1 diabetes mellitus (T1DM) comparing the safety and efficacy of MYL-1601D with NovoLog. After screening period of up to 3 weeks, all subjects were titrated on NovoLog during a 4-week run-in period and were shifted from their current basal insulin to study insulin Lantus. After the run-in period, subjects were randomized; 1 group received MYL-1601D, while the other group received NovoLog for 24 weeks. A follow-up visit, via telephone call, was scheduled within 4 weeks after last dose of MYL-1601D.

The ITT set consisted a total of 478 patients (238 in the MYL-1601D and 240 in the NovoLog group). The primary efficacy analysis was conducted using the ITT population.

In the MYL-1601D group, the mean (SD) age was 44.5 (13.33) years, 54.2% of subjects were male, and 45.8% were female. The majority of subjects (210 [88.2%] subjects) were White and 23.9% of subjects were of Hispanic or Latino ethnicity. In the NovoLog group, the mean (SD)

age was 44.2 (13.91) years, 55.0% of subjects were male, and 45.0% were female. The majority of subjects (210 [87.5%] subjects) were White and 18.8% of subjects were of Hispanic or Latino ethnicity. The mean (SD) duration of diabetes at baseline was 22.3 (13.71) years in the MYL-1601D group and 21.3 (12.91) years in the NovoLog group. Overall, the baseline disease characteristics of the 2 treatment groups were similar.

The study met its primary endpoint demonstrating that immunogenicity, as assessed by treatment emergent antibody response (TEAR) rate, was comparable between the MYL-1601D and NovoLog during 24-week treatment. TEAR positive rate was similar between the MYL-1601D (59 [24.9%] subjects) and NovoLog (67 [27.8%] subjects) groups.

15.2.1.2 Immunogenicity

In Study MYL-1601D-3001, the cumulative at any visit from baseline (inclusive) to week 24, ADA positive samples were identified in 210 (88.2%) subjects in MYL-1601D group and 202 (84.2%) subjects in NovoLog group. Out of those ADA positive samples, NAb positive were seen in 33 (13.9%) subjects in MYL-1601D and 30 (12.5%) subjects in NovoLog group. At baseline visit, prior to MYL-1601D treatment, there were 189 (79.4%) and 170 (70.8%) subjects that were ADA positive in MYL-1601D and Novolog group respectively, out of these subjects 15 (6.3%) and 17 (7.1%) subjects were NAb positive at baseline in MYL-1601D and Novolog group respectively.

16 COMPARATIVE NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY

16.1 Comparative Non-Clinical Pharmacodynamics

The pharmacodynamic response to Kirsty (insulin aspart) (also referred to as MYL-1601D) and reference insulin aspart (US-NovoLog and/or EU-NovoRapid) was compared in *in vitro* studies.

Over the course of Kirsty's development, a comprehensive non-clinical evaluation of comparative pharmacodynamics was conducted with MYL-1601D and reference insulin aspart. These studies were designed considering the mechanism of action of insulin aspart and included the following *in vitro* assays:

- Insulin Receptor-A binding kinetics
- Insulin Receptor-B binding kinetics
- Insulin Receptor-A phosphorylation
- Insulin Receptor-B phosphorylation
- Cell-based assays for metabolic activity
    - Glucose uptake
    - Inhibition of stimulated lipolysis
    - Adipogenesis
- IGF-1R binding kinetics
- Cell based assay of mitogenic activity

The results of each *in vitro* study demonstrated that MYL-1601D was similar to reference insulin aspart.

16.2 Comparative Toxicology

Two comparative toxicology studies were conducted with MYL-1601Dand US reference insulin aspart. The first study evaluated potential systemic toxicity in rats after a single intravenous dose of 0 (vehicle), 4.4, 8.8, or 17.5 mg/kg followed by a 14-day observation period. All animals treated with MYL-1601D or reference insulin aspart exhibited fine tremors and rapid respiration immediately after dosing. Additionally, in all test article treated animals, somnolence was observed at 0.5 to 1-hour post dose. These phenotypic signs were attributed to hypoglycemia, an expected pharmacodynamic effect. No other clinical signs or toxicity findings were observed.

In a comparative repeat-dose toxicity study, rats were administered MYL-1601D or reference insulin aspart at doses of 0.105, 0.315, or 1.05 mg/kg twice per day (equal to 0.21, 0.63, or 2.1 mg/kg per day) by subcutaneous injection for 28 days with a 14-day recovery period. An additional group of rats was administered vehicle.

Female rats administered MYL-1601D or reference insulin aspart showed reduced motor activity, potentially from hypoglycemia, which is consistent with the pharmacological activity of insulin aspart. Overall, rats administered MYL-1601D or reference insulin aspart demonstrated similar toxicity and local tolerability, with no systemic adverse effects or unique toxicities identified for MYL-1601D.

MYL-1601D and reference insulin aspart were similarly effective at reducing blood glucose, an anticipated pharmacodynamic effect. The reduction in serum glucose was of comparable magnitude and duration in both MYL-1601D and reference insulin aspart treated animals across dose levels. Anti-drug antibody development was not assessed.

17 CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG

Postprandial and overall glycemic control: In diabetic patients, insulin aspart 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 insulin aspart, significantly improved metabolic control was obtained compared to regular human insulin after 6 months treatment, the values being 7.78±0.03% for insulin aspart and 7.93±0.05% ($p < 0.01$) for regular human insulin in one trial and correspondingly 7.88±0.03% and 8.00±0.04% ($p<0.02$) in the other trial. This improvement in glycemic control with insulin aspart 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, insulin aspart 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 -1.46mmol/L in one trial and -1.15 mmol/L in the other; $p<0.0001$).

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

Type 1 Diabetes:

Continuous subcutaneous insulin infusion (CSII) – Pump:
To evaluate the use of insulin aspart by continuous subcutaneous insulin infusion (CSII) with an external pump, one open-label, randomized, parallel design study for 16 weeks [n=118][4] compared insulin aspart 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]. Insulin aspart by CSII was compared to a basal/bolus regimen of pre-prandial insulin aspart and basal Novolin®ge NPH injections. Reductions in A1C and rates of hypoglycemia were comparable. In the study (insulin aspart versus Humalog®), the rate of clogging or blockage events was similar between insulin aspart and Humalog®.

Pregnancy
The safety and efficacy of an intensified insulin regimen with insulin aspart was studied in an open-label study in 157 pregnant women with type 1 diabetes. 72% (113) were pregnant prior to entering the study (PBS) and 28% (44) entered the study before conception (PAS). The entry criteria for A1C were different between PBS and PAS (<8% vs. < 12%). PAS patients were withdrawn if A1C was > 8% at conception, so in this subgroup only women who conceived and had A1C < 8% had efficacy and safety parameters evaluated. The proportions of patients reaching different A1C targets with insulin aspart are presented in the following Table 3.

Table 3: Summary of A1C (%) by Pregnancy status at Screening - ITT Pregnant

Number of patients	Pregnant at Screening 113			Pregnant after Screening 44			ITT Pregnant 157		
	P	N	%	P	N	%	P	N	%
Visit P2 (week 12)									
A_{1c} ≤6.0%	108	36	33.3	31	9	29.0	*	*	*
A_{1c} ≤6.5%	108	70	64.8	31	21	67.7	*	*	*
A_{1c} ≤7.0%	108	98	90.7	31	26	83.9	*	*	*
Visit P3 (week 24)									
A_{1c} ≤6.0%	102	66	64.7	31	13	41.9	133	79	59.4
A_{1c} ≤6.5%	102	83	81.4	31	27	87.1	133	110	82.7
A_{1c} ≤7.0%	102	96	94.1	31	30	96.8	133	126	94.7
Visit P3 (week 36)									
A_{1c} ≤6.0%	96	53	55.2	26	7	26.9	122	60	49.2
A_{1c} ≤6.5%	96	77	80.2	26	18	69.2	122	95	77.9
A_{1c} ≤7.0%	96	90	93.8	26	26	100.0	122	116	95.1

Follow-up Visit (6 weeks postpartum)									
A_{1c} ≤6.0%	104	35	33.7	36	8	22.2	140	43	30.7
A_{1c} ≤6.5%	104	58	55.8	36	20	55.6	140	78	55.7
A_{1c} ≤7.0%	104	80	76.9	36	26	72.2	140	106	75.7

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

Major and minor hypoglycemia rates for PBS and PAS by trimester are presented in the following Table 4.

Table 4: All Treatment Emergent Hypoglycemic Episodes During Pregnancy by Treatment, pregnancy status at Screening and trimester - ITT Pregnant.

		lAsp + NPH				
		P	N	%	E	Rate
Major	Pregnant at Screening					
	1. trimester	113	19	(16.80)	34	5.2
	2. trimester	113	22	(19.50)	44	1.3
	3. trimester	113	9	(8.00)	20	1
	Pregnant after Screening					
	1. trimester	44	5	(11.40)	7	0.8
	2. trimester	44	5	(11.40)	7	0.7
	3. trimester	44	1	(2.30)	1	0.2
	All					
	1. trimester	157	24	(15.30)	41	2.7
	2. trimester	157	27	(17.20)	51	1.2
	3. trimester	157	10	(6.40)	1	0.8
Minor	Pregnant at Screening					
	1. trimester	113	97	(85.80)	907	139.4
	2. trimester	113	98	(86.70)	2992	90.9
	3. trimester	113	85	(75.20)	1639	83.7
	Pregnant after Screening					
	1. trimester	44	40	(90.90)	607	69.3
	2. trimester	44	33	(75.00)	672	68.1
	3. trimester	44	27	(61.40)	380	67.4
	All					
	1. trimester	157	137	(87.30)	1514	98.9
	2. trimester	157	131	(83.40)	3664	85.7
	3. trimester	157	112	(71.30)	2019	80.1
Symptoms Only	Pregnant at Screening					

		lAsp + NPH				
		P	N	%	E	Rate
	1. trimester	113	32	(28.300	154	23.5
	2. trimester	113	40	(35.40)	407	12.4
	3. trimester	113	34	(30.10)	256	13.1
	Pregnant after Screening					
	1. trimester	44	24	(54.50)	85	9.7
	2. trimester	44	15	(34.10)	118	12
	3. trimester	44	11	(25.00)	35	6.2
	All					
	1. trimester	157	56	(35.70)	39	15.6
	2. trimester	157	55	(35.00)	525	12.3
	3. trimester	157	45	(28.70)	291	11.5
Unclassifiable	Pregnant at Screening					
	1. trimester	113	4	(3.50)	11	1.7
	2. trimester	113	9	(8.00)	58	1.8
	3. trimester	113	6	(5.30)	34	1.7
	Pregnant after Screening					
	1. trimester	44	4	(9.10)	6	0.7
	2. trimester	44	4	(9.10)	6	0.6
	3. trimester	44	3	(6.80)	27	4.8

P: Number of patients in the Population
N: Number of patients having Hypoglycemic Episodes
%: Proportion of patients in the Population having Hypoglycemic Episodes
E: Number of Hypoglycemic Episodes
Rate: Number of Hypoglycemic Episodes divided by years of exposure of patients in the Population in the given trimester

The outcome data observed in the human insulin control arm in the insulin aspart 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, 2- period, cross-over study showed that 4-hour postprandial glucose excursion in 37 patients (BMI 27.05±4.02, waist circumference 97.1±11.7 cm) was 20% lower following a single injection of insulin aspart (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 insulin aspart (p=0.023) and was reached 27 minutes earlier (p=0.039), despite the fact that insulin aspart was injected 30 minutes after human insulin.

In 182 type 2 diabetic patients treated with insulin aspart in a meal-related regimen for 6 months, the pharmacodynamic properties of insulin aspart 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 300-600 minutes post dosing. The pharmacodynamic response to a single 0.3 U/kg dose of IAsp and a single 0.3 IU/kg was evaluated during euglycaemic clamp procedures in a cross-over design. Consistent with the pharmacokinetic results, the peak pharmacodynamic activity as determined by maximum value on the glucose infusion rate (GIR) profile was significantly higher (p=0.0039) and occurred approximately 83 minutes earlier with IAsp than with HI (p<0.0001). The area under the GIR profiles in the interval from 0-120 minutes was on average more than twice as large with IAsp than with HI and this difference was statistically significant (p<0.0001). Overall, the pharmacokinetic and pharmacodynamic properties of IAsp are preserved in geriatric patients with type 2 diabetes although a minor delay in peak insulin concentration has been observed when compared with younger patients with type 2 diabetes.

Combination with long-acting basal insulin analog: In an open-label, parallel, randomized trial involving 595 patients with type 1diabetes, insulin aspart 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 insulin aspart/ 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 insulin aspart 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, insulin aspart significantly reduced the rate of minor hypoglycemic events when with the rate of minor events was significantly reduced by 7% with insulin aspart 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 insulin aspart while maintaining overall glycemic control. The mean A1C remained constant, with values being 7.69% for insulin aspart 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 insulin aspart compared to regular human insulin.

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

18 NON-CLINICAL TOXICOLOGY – REFERENCE BIOLOGIC DRUG

DETAILED PHARMACOLOGY

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

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

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

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

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

The performed bioassays show that the potency of insulin aspart is equal to that of human insulin.

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

Test	**Insulin Aspart / Human Insulin (HI)**	**Results**
Irwin Observation Test, mice	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No difference from human insulin was observed
Locomotor Activity, rats	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No consistent effect
Rotarod Performance, mice	1,10 or 100 U/kg IV, HI 100 IU/kg IV	No effects

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

There was no significant difference in pharmacokinetics in a trial in type 2 diabetic patients. No significant difference in efficacy, as assessed by A1C was found between genders in a trial in 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 5: Results of Acute Toxicity Studies with Insulin Aspart

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

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

Long-term Toxicity:

Table 6: Results of long-term toxicity studies with insulin aspart.

Species	Strain	Number of groups and size	Dosing Method	Dosing Method	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.

Species	Strain	Number of groups and size	Dosing Method	Dosing Method	Dose level (U/kg/day)	Results
Rat	Sprague-Dawley	4 Groups 10M, 10F	SC	4 weeks	0, 12.5, 50, 200	Hypoglycemia. No unexpected observations.
Rat	Mol: WIST	4 Groups 15M, 15F	SC	13 weeks	0, 12.5, 50, 200	Hypoglycemia, increased weight gain. No unexpected observations.
Rat	Sprague-Dawley	4 Groups 32M, 32F Satellites included	SC	52 weeks	**Top dose levels** 100 bid for 24 weeks, 50 bid weeks 25-26, 100 od weeks 27-37, 75 od from week 38-52. **Lower dose levels** 5 and 25U/kg/bid for 26 weeks 10 and 50 od for 27-52 weeks Controls.	Hypoglycemia, increased food and water consumption and weight gain. Excess of mammary tumours in high dose females.
Rat	Sprague-Dawley	4 Groups 20F	SC	52 weeks	200 per drug substance. Insulin aspart, human insulin, control.	Mammary tumour-incidence higher in insulin aspart group equal to human insulin both being higher than controls.
Dog	Beagle	4 groups 3M, 3F/group, main 1M, 1F in groups 1 & 4 reversibility assessment	SC	4weeks (+ 4 Week recovery in groups 1 & 4)	0, 0.25, 0.5, 1.0 bid	Hypoglycemia. No unexpected observations.
Dog	Beagle	3 Groups	SC	13 weeks	0,1, 4	Hypoglycemia.

Species	Strain	Number of groups and size	Dosing Method	Dosing Method	Dose level (U/kg/day)	Results
		4M, 4F				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 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 insulin aspart differed from those observed with regular human insulin. In vitro trials showed that the mitogenicity of insulin aspart does not differ from that observed with regular human insulin. Animal trials on the mutagenic potential of insulin aspart and regular human insulin did not show any difference between the two products.

Mutagenicity:
A comprehensive range of experiments have been completed and, insulin aspart gave negative results. Human insulin also gave negative results. It is concluded that insulin aspart is not a genotoxicant.

19 SUPPORTING PRODUCT MONOGRAPHS

1. NovoRapid® (Solution for Injection, 100 Units / mL), submission control 251029, Product Monograph, Novo Nordisk Canada Inc. August 12, 2021

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Kirsty®
Insulin Aspart Injection

Read this carefully before you start taking **Kirsty®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Kirsty®**.

Kirsty® is a biosimilar biologic drug (biosimilar) to the reference biologic drug NovoRapid. A biosimilar is authorized based on its similarity to a reference biologic drug that was already authorized for sale.

Contact your doctor, Diabetes Nurse Educator or pharmacist if you have any questions about this drug.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, Diabetes Nurse Educator or your pharmacist. If you have trouble reading this, ask a family member or a friend for help.

Serious Warnings and Precautions

- Hypoglycemia is the most common adverse effect of insulin, including Kirsty®.
- If hypoglycemia or hypoglycemic reactions are not treated they can result in the loss of consciousness, coma or death.
- Glucose monitoring is recommended for all patients with diabetes.
- Any change of insulin should be made cautiously and only under medical supervision. This may result in dosage adjustment.
- Kirsty® should be given immediately before a meal because of the fast onset of action (start of the meal should be not more than 5-10 minutes after injection). (see 'How to take Kirsty®')
- Never inject your insulin directly into a vein.
- Kirsty® should not be used if it is not water-clear and colourless.

What is Kirsty® used for?

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

How does Kirsty® work?

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

What are the ingredients in Kirsty®?

Medicinal ingredients: The active ingredient in Kirsty® is insulin aspart.
Non-medicinal ingredients: Disodium hydrogen phosphate dihydrate; glycerol; metacresol;

phenol; sodium chloride; water for injection and zinc chloride. Hydrochloric acid and sodium hydroxide are used for pH adjustment.

Kirsty® comes in the following dosage forms:

- Kirsty® 10 mL vial
- Kirsty® 3 mL prefilled pen

Do not use Kirsty® if:

- You feel hypoglycemic reaction (low blood sugar) coming on. (see "*What are possible side effects from Kirsty®?*" for more about hypoglycemia).
- You are allergic (hypersensitive) to insulin aspart, metacresol or any of the other ingredients in this insulin. Look out for the signs of an allergic reaction. (see "What are possible side effects from Kirsty®?")
- The protective cap is loose or missing. Each vial has a protective, tamper proof plastic cap. If the cap is not in perfect condition when you get the vial, return the vial to your supplier.
- The insulin has not been stored correctly or if it has been frozen. (see "*How to store Kirsty®*")
- The insulin does not appear water-clear and colourless.

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

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Kirsty®. Talk about any health conditions or problems you may have, including if you:

- Have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands, your doctor may decide to alter your insulin dose.
- Drink alcohol (including wine and beer) your need for insulin may change as your blood sugar level may either rise or fall.
- Have an infection, fever or have had an operation you may need more insulin than usual.
- Suffer from diarrhea, vomiting or eat less than usual you may need less insulin than usual.
- Exercise more than usual or if you want to change your usual diet.
- Are ill: continue taking your insulin. Your need for insulin may change.
- Go abroad: travelling over time zones may affect your insulin needs and the timing of your injections. Consult your doctor if you are planning such travel.
- Are pregnant, or planning a pregnancy or are breastfeeding please contact your doctor for advice.
- Drive or use tools or machines: watch for signs of a hypoglycemia. Your ability to concentrate or to react will be less during a hypoglycemic reaction. Please keep this in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). Never drive or use machinery if you feel a hypoglycemic reaction coming on.

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

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

Thiazolidinediones (class of oral antidiabetic drugs) used together with insulin may increase risk

of oedema and heart failure. Inform your doctor as soon as possible if you experience localised swelling (oedema) or signs of heart failure such as unusual shortness of breath.

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

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

Other warnings you should know about:

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

- **Skin changes at the injection site**: The injection site should be rotated to help prevent changes to the fatty tissue under the skin, such as skin thickening, skin shrinking or lumps under the skin. The insulin may not work very well if you inject into a lumpy, pitted, or thickened area. Tell your healthcare professional if you notice any skin changes at the injection site. Tell your healthcare professional if you are currently injecting into these affected areas before you start injecting in a different area. A sudden change of site may result in hypoglycemia. Your healthcare professional may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

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

The following may interact with Kirsty®:
Some medicines affect the way glucose works in your body and this may influence your insulin dose. Listed below are the most common medicines, which may affect your insulin treatment. Tell your doctor, Diabetes Nurse Educator or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. In particular, you should tell your doctor if you are using any medicine as mentioned below that affects your blood sugar level.

If you take any of the medicines below, your blood sugar level may fall (hypoglycemia)

- Other medicines for the treatment of diabetes
- Monoamine oxidase inhibitors (MAOI) (used to treat depression)
- Beta-blockers (used to treat high blood pressure)
- Angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure)
- Salicylates (used to relieve pain and lower fever)
- Anabolic steroids (such as testosterone)
- Sulfonamides (used to treat infections)

If you take any of the medicines below, your blood sugar level may rise (hyperglycemia)

- Oral contraceptives (birth control pills)
- Thiazides (used to treat high blood pressure or excessive fluid retention)
- Glucocorticoids (such as 'cortisone' used to treat inflammation)
- Thyroid hormones (used to treat thyroid gland disorders)

- Sympathomimetics (such as epinephrine [adrenaline], or salbutamol, terbutaline used to treat asthma)
- Growth hormone (medicine for stimulation of skeletal and somatic growth and pronounced influence on the body's metabolic processes)
- Danazol (medicine acting on ovulation)

Octreotide and lanreotide (used for treatment of acromegaly, a rare hormonal disorder that usually occurs in middle-aged adults, caused by the pituitary gland producing excess growth hormone) may either increase or decrease your blood sugar level.

Beta-blockers (used to treat high blood pressure) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycemia.

How to take Kirsty®:
Kirsty® is for injection under the skin (subcutaneously).

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

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

You should always measure your blood glucose regularly.

Talk about your insulin needs with your doctor and Diabetes Nurse Educator. Do not change your insulin unless your doctor tells you to. Follow their advice carefully. This leaflet is a general guide only. If your doctor has switched you from one type or brand of insulin to another, your dose may have to be adjusted by your doctor.

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

Before using Kirsty®
- Check the label to make sure you have the right type of insulin.
- Remove the protective cap.
- Always use a new needle for each injection to prevent contamination.
- Needles and syringes must not be shared. Do not reuse or share needles with another person including family members. You may give another person an infection or get an infection from them.
- Kirsty® pre-filled pen is only suitable for injecting under the skin. Speak to your doctor if you need to inject your insulin by another method.

Always use your insulin and adjust your dose exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

If you use only one type of insulin [vial]

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

How to inject this insulin [vial]

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

For use in an infusion pump system [vial]:
Kirsty® should never be mixed with any other insulin when used in a pump.
Follow the instructions and recommendations from your doctor regarding the use of Kirsty® in a pump. Before using Kirsty® in a pump system you must receive comprehensive instructions in its use and information about any actions to be taken in case of illness; too high or too low blood sugar; or failure of the pump system.

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

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

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

How to inject this insulin [pre-filled pen]

- Kirsty® is for injection under the skin (subcutaneously). You must never inject yourself directly into vein (intravenously) or muscle (intramuscularly). Use the injection technique advised by your healthcare professional.
- Keep the needle under your skin for at least six seconds. Keep the push button fully depressed until the needle has been withdrawn. This will ensure correct delivery and limit possible flow of blood into the needle or insulin reservoir.
- After each injection be sure to discard the needle. Otherwise, the liquid may leak out when the temperature changes.

Overdose:

If you think you have taken too much Kirsty®, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Causes of a hypoglycemia:
You get a hypoglycemia if your blood sugar gets too low.
This might happen:

- If you take too much insulin.
- If you eat too little or miss a meal.
- If you exercise more than usual.

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

If you get any of these signs: eat glucose tablets or a high sugar snack (sweets, biscuits, fruit juice), then rest. Don't take any insulin if you feel a hypoglycemia coming on. Carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.

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

- If severe hypoglycemia is not treated, it can cause brain damage (temporary or permanent) and even death.
- If you have a hypoglycemia that makes you pass out, or if you get a lot of hypoglycemias, talk to your doctor. The amount or timing of your insulin dose, the amount of food you eat or the amount of exercise you do, may need to be adjusted.

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

Causes of a hyperglycemia:
You get a hyperglycemia if your blood sugar gets too high.
This might happen:

- If you forget to take insulin.
- If you repeatedly take less insulin than you need.
- If you eat more than usual.
- If you exercise less than usual.

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

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

If you get any of these signs: test your blood sugar level; test your urine for ketones if you can;

then seek medical advice right away.

What are possible side effects from using Kirsty®?

These are not all the possible side effects you may feel when taking Kirsty®. If you experience any side effects not listed here, contact your healthcare professional.

Like all medicines, Kirsty® can cause side effects, although not everybody gets them. The most common side effect is low blood sugar (hypoglycemia). See the advice in 'How to take Kirsty®?'.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
LESS COMMON (1 to 10 users in 1000)			
Signs of allergy: Hives and rash may occur.		√	√
Vision problems: disruption of vision when treatment is first started (temporary).	√		
Changes at the injection site (lipodystrophy): Lipoatrophy or lipohypertrophy.		√	
Swollen joints: When you start taking in insulin, water retention may cause swelling around your ankles and other joints. This soon disappears	√		
Diabetic retinopathy (eye background changes): If you have diabetic retinopathy and your blood glucose levels improve very fast, the retinopathy may get worse.		√	
RARE (less than 1 user in 10,000)			
Painful neuropathy	√		

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
(nerve related pain): If your blood glucose levels improve very fast you may get nerve related pain. This is called acute painful neuropathy and is usually transient.			
UNKNOWN			
Cutaneous Amyloidosis: Lumps under skin.		√	

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

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep out of the reach and sight of children. Keep Kirsty® protected from heat or light.

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

10 mL vial:

Before opening: Store in a refrigerator at 2°C to 8°C, away from the cooling element. Do not freeze. Protect from light.

During use or when carried as a spare: Store below 30°C. The product may be stored for a maximum of 4 weeks. Do not refrigerate or freeze

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

Pre-filled pen:

Before opening: Kirsty® pre-filled pen that is not being used is to be stored in the refrigerator at 2°C to 8°C, away from the cooling element. Do not freeze.

During use or when carried as a spare: You can carry your Kirsty® pre-filled pen with you and keep it at a temperature below 30°C or in a refrigerator (2˚C to 8˚C) for up to 4 weeks. If refrigerated, keep away from the cooling element. Do not freeze.

The Kirsty® pre-filled pen you are using should be thrown away after 4 weeks, even if it still has insulin left in it. Do not use this medication after the expiration date stated on the label.

What Kirsty® looks like and package content
Kirsty® comes as a water-clear, colourless, aqueous solution in packages of one 10 mL vial per carton.

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

1 mL contains 100 U (units) of insulin aspart.
1 vial contains 10 mL of insulin aspart equivalent to 1000 U.
1 prefilled pen contains 3 mL insulin aspart equivalent to 300 U.

If you want more information about Kirsty®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website BGP Pharma ULC, or by calling 1-844-596-9526

This leaflet was prepared by BGP Pharma ULC, Etobicoke, Ontario, M8Z 2S6
Prepared on: October 12, 2021

Instructions for Use:

Kirsty® pre-filled pen

Read the following instructions carefully before using your Kirsty® pre-Filled pen. If you do not follow the instructions carefully, you may get too little or too much insulin, which can lead to too high or too low blood sugar level.

Do not use the pen without proper training from your doctor or nurse. If you are blind or have poor eyesight and cannot read the dose counter on the pen, do no use this pen without help. Get help from a person with good eyesight who is trained to use the pre-filled pen.

Kirsty® pre-filled Pen is a prefilled dial-a-dose insulin pen. You can select doses from 1 to 80

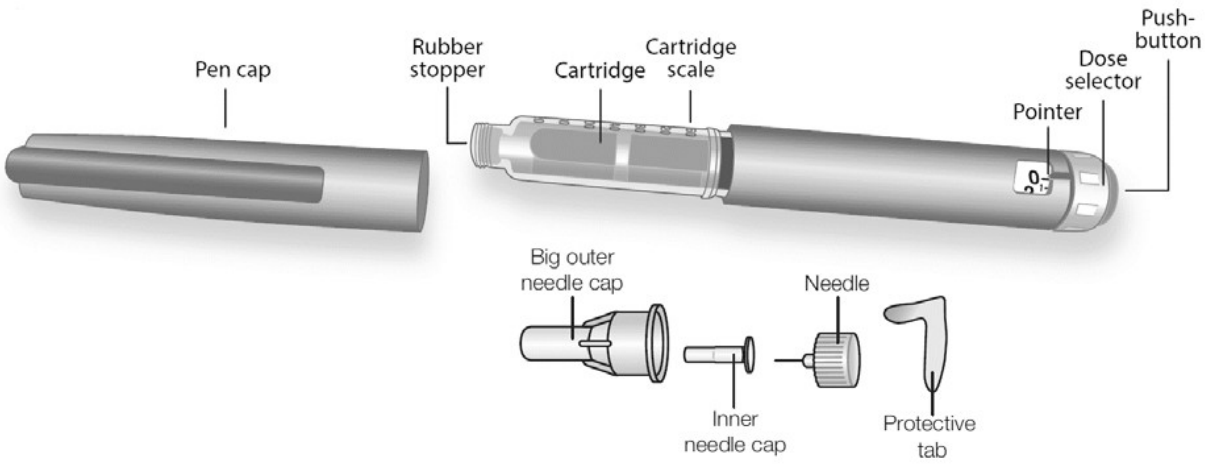
units in increments of 1 unit.

Needle sizes compatible with this pen:

- 31G, 5 mm
- 32G, 4 mm
- 34G, 4mm

As a precautionary measure, always carry a spare insulin delivery device in case you Kirsty® pre-filled pen is lost or damaged.

Kirsty® pre-filled pen



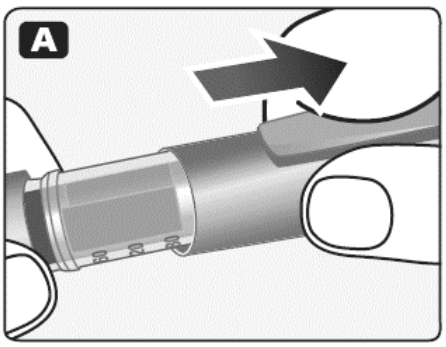
Preparing your Kirsty® pre-filled pen

Wash your hands before using the pen.

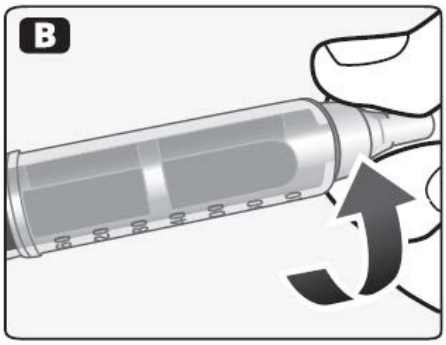
Check the name (Kirsty) on the label of your blue pen with orange button to make sure that it contains the correct type of insulin. This is especially important if you take more than one type of insulin. If you take the wrong type of insulin, your blood sugar level may get too high or too low.

Check the insulin in the cartridge. Kirsty® should be clear, colourless and free of particles. If not, do not use.

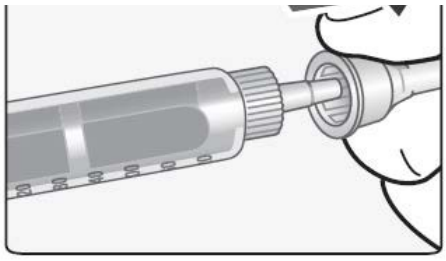
A. Pull off the pen cap.
Wipe the rubber stopper with an alcohol swab.



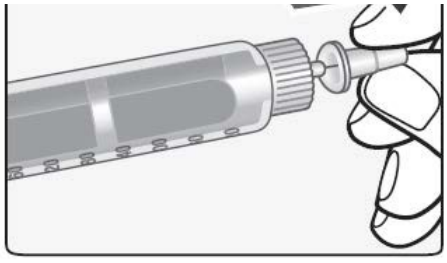
B. Remove the paper tab from a new disposable needle.
Screw the needle straight and tightly onto your Kirsty® pre-filled pen.



C. Pull off the big outer needle cap and keep it for later.



D. Pull off the inner needle cap and dispose of it. Never try to put the inner needle cap back on the needle. You may stick yourself with the needle.



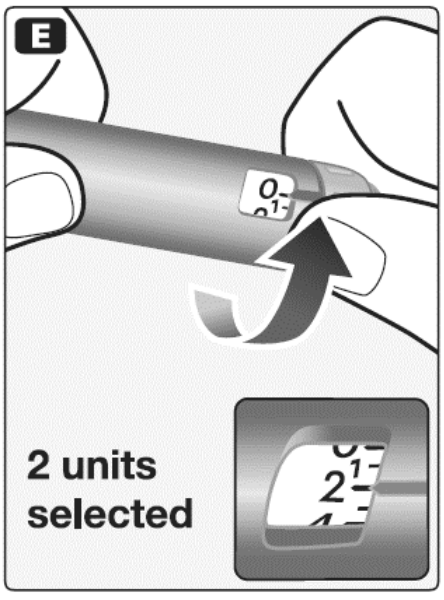
⚠ Always use a new needle for each injection. This reduces the leakage of insulin, blocked needles and inaccurate dosing.

⚠ Be careful not to bend or damage the needle before use.

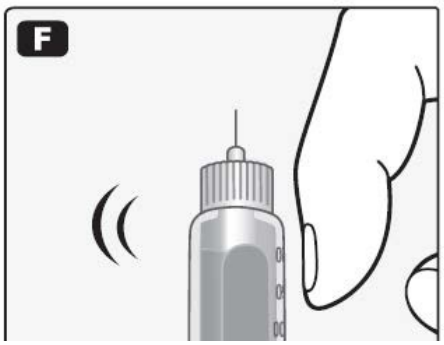
Checking the insulin flow

Prior to each injection small amounts of air may collect in the cartridge during normal use. To avoid injection of air and ensure proper dosing:

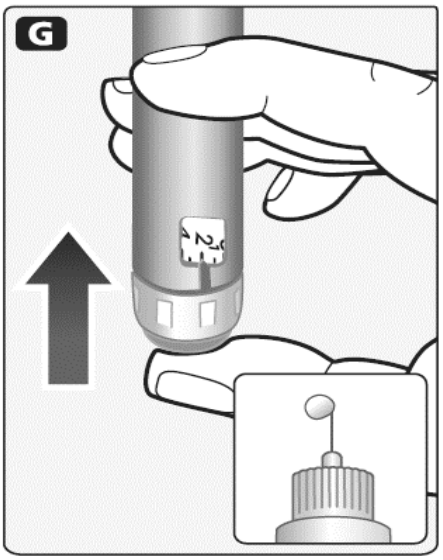
E. Turn the dose selector to select 2 units.



F. Hold your Kirsty® pre-filled pen with the needle pointing upwards and tap the cartridge gently with your finger a few times to make any air bubbles collect at the top of the cartridge.



G. Keeping the needle upwards, press the push-button all the way in. The dose selector returns to 0. A drop of insulin should appear at the needle tip. If not, change the needle and repeat the procedure no more than 6 times.
If a drop of insulin still does not appear, the pen is defective, and you must use a new one.



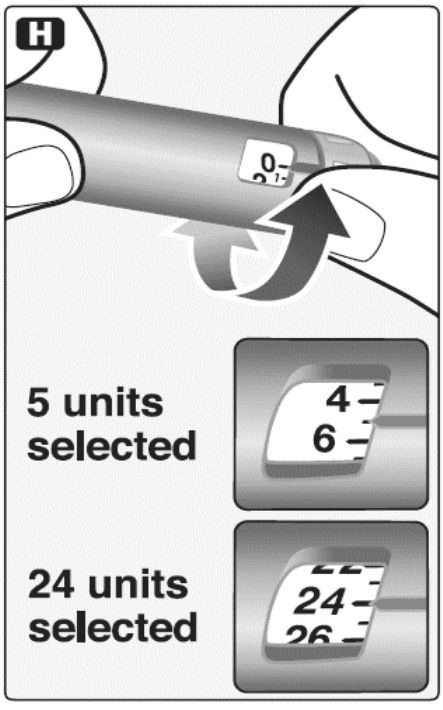
⚠ Always make sure that a drop appears at the needle tip before the insulin flows. If no drop appears, you will not inject any insulin, may move. This may indicate a blocked or damage needle.

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

Selecting your dose

Check that the dose selector is set at 0.

H. Turn the dose selector to the number of units you need to inject.
The dose can be corrected either up or down by turning the dose selector in either direction until the correct dose lines up with the pointer. When turning the dose selector, be careful not to push the push-button as insulin will come out.
You cannot select a dose larger than the number of units left in the cartridge.



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

⚠ Do not count the pen clicks. If you select and inject the wrong dose, your blood sugar level may get too high or too low. Do not use the residual scale, it only shows approximately how much insulin is left in your pen.

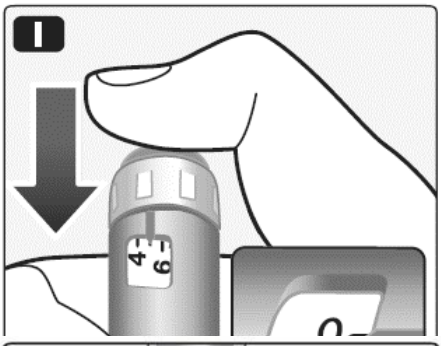
Giving the injection

Use the injection technique shown by your doctor or nurse.
Kirsty® can be injected under the skin (subcutaneously) of your stomach area, buttocks, upper legs (thighs) or upper arms.

For each injection change (rotate) your injection site within the area of skin that you use. **Do not** use the same injection site for each injection.

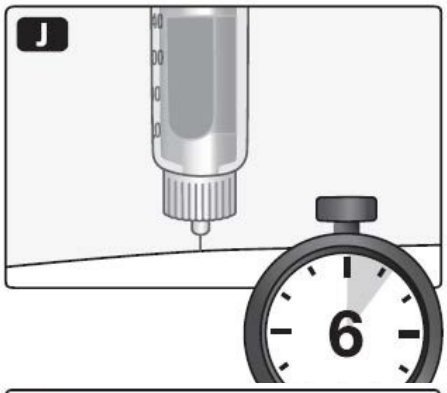
I. Insert the needle into your skin. Inject the dose by pressing the push-button all the way in until 0 lines up with the pointer. Be careful only to push the push-button when injecting.

Turning the dose selector will not inject insulin.

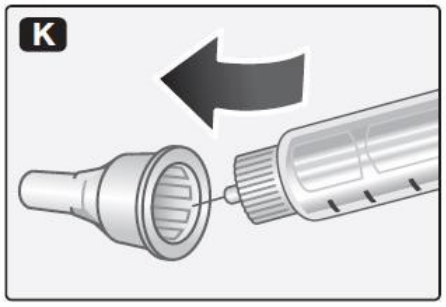


J. Keep the push-button fully depressed and let the needle remain under the skin for at least 6 seconds. This will make sure you get the full dose. Withdraw the needle from the skin, then release the pressure on the push-button.

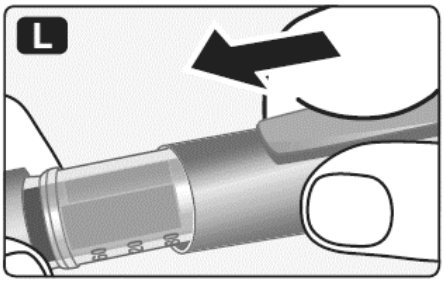
Always make sure that the dose selector returns to 0 after the injection. If the dose selector stops before it returns to 0, the full dose has not been delivered, which may result in too high blood sugar level.



K. Lay the outer needle cap on a flat surface and carefully insert the needle into the cap. Do not touch the needle. Once the needle is covered push the cap on and unscrew the needle.
Safely remove the needle from your Kirsty® pre-filled pen after each use.
Dispose of needle in a suitable sharp's container.



Put the pen cap on the Kirsty® pre-filled pen and store the pen without the needle attached.



Caring for your pen

Your Kirsty® pre-filled pen must be handled with care. If it is dropped, damaged, or crushed, there is a risk of insulin leakage. This may cause inaccurate dosing, which can lead to too high or too low blood sugar level.

You can clean the exterior of your Kirsty® pre-filled pen by wiping it with a medicinal swab. Do not soak it, wash or lubricate it as it may damage the pen.

Do not refill your Kirsty® pre-filled pen. Once empty, it must be disposed of.

Important information

- Always keep your pen with you.
- Always carry an extra pen and new needles with you. In case of loss of damage.
- Always keep your pen and needles out of sight and reach of others, especially children.
- Never share your pen or your needles with other people. It might lead to cross-infection.
- Never share your pen with other people. Your medicine might be harmful to their health.
- Caregivers must be very careful when handling used needles to reduce the risk of needle injury and cross-infection.