PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

TRURAPI®

insulin aspart injection

Solution for Injection, 100 Units/mL, subcutaneous

Manufacturer Standard

Anti-diabetic Agent

ATC Code: A10AB05
Fast-acting insulin analogue

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RECENT MAJOR LABEL CHANGES

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Sections or subsections that are not applicable at the time of authorization are not listed.

Trurapi® (insulin aspart injection) 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 Trurapi and the reference biologic drug NovoRapid.

Trurapi (insulin aspart injection) is indicated for:

- the treatment of patients with diabetes mellitus who require insulin for the control of hyperglycemia.
- Trurapi should normally be used in regimens together with an intermediate or long-acting insulin.

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

1.1 Pediatrics

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 10 CLINICAL PHARMACOLOGY.

1.2 Geriatrics

There was no clinically relevant difference in the pharmacokinetics and pharmacodynamics of insulin aspart between elderly and younger subjects. Please see 7 WARNINGS AND PRECAUTIONS and 10 CLINICAL PHARMACOLOGY.

2 CONTRAINDICATIONS

Trurapi is contraindicated:

- In patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- During episodes of hypoglycemia.

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 5 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 7 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 **Error! Not a valid bookmark self-reference.**).
- Short-acting insulin should be combined with a longer-acting insulin to maintain adequate glucose control (see 4 **Error! Not a valid bookmark self-reference.**).
- Insulin products shall not be mixed with any other insulin unless clearly indicated and done under medical supervision (see 7 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 **Error! Not a valid bookmark self-reference.**).

4 DOSAGE AND ADMINISTRATION

The Trurapi cartridges should only be used with the following pens:
- JuniorSTAR which delivers Trurapi in 0.5 unit dose increments
- AllStar PRO which delivers Trurapi in 1 unit dose increments

These cartridges should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pens.

4.1 Dosing Considerations

Substances added to Trurapi may cause degradation of insulin aspart.

This medicinal product must not be diluted or mixed with other medicinal products, except with intravenous infusion fluids.

- Patients being initiated on insulin can be started on Trurapi in the same manner as they would be on animal-source or human insulin.
- Changes for patients being transferred from other insulin to Trurapi should be made as directed by a physician.
- Trurapi vial can be used for continuous subcutaneous insulin infusion (CSII) in pump systems.
- Trurapi vial can also be used for intravenous administration of insulin aspart, by physicians or other healthcare professionals, as applicable.

Transition from reference product to Trurapi
- Transferring a patient from NovoRapid® to Trurapi can be done unit-to-unit based on the previous fast-acting insulin dose.

4.2 Recommended Dose and Dosage Adjustment

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

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

The dosing of Trurapi 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.

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.

4.4 Administration

Trurapi (insulin aspart injection) is administered subcutaneously by injection in the abdominal wall, the thigh, the upper arm, the deltoid region or the gluteal region. Injection sites must 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 to reduce the risk of lipodystrophy and localized cutaneous amyloidosis. Do not inject into areas of lipodystrophy or localized cutaneous amyloidosis (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONSADVERSE REACTIONS). Trurapi 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 discolouration prior to administration, whenever solution and container permit. Never use Trurapi if it has become viscous (thickened) or cloudy; use it only if it is water-clear and colourless. Trurapi 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.

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 an extra pen, insulin and needles in case they get lost or damaged.

Continuous Subcutaneous Insulin Infusion (CSII)
Trurapi may be used for CSII in pump systems suitable for insulin infusion. CSII should be administered in the abdominal wall. Infusion sites should be rotated.

When used with an insulin infusion pump, Trurapi should not be mixed with any other insulin medicinal products.

Patients using CSII should be comprehensively instructed in the use of the pump system and use the correct reservoir and tubing for the pump (see 12 SPECIAL HANDLING INSTRUCTIONS). The infusion set (tubing and cannula) should be changed in accordance with the instructions in the product information supplied with the infusion set.

Patients administering Trurapi by CSII must have an alternative insulin delivery method available in case of pump system failure.

Intravenous use
If necessary, Trurapi can be administered intravenously by physicians or other healthcare staff. Monitoring of blood glucose is necessary during insulin infusion. For intravenous use, infusion systems with Trurapi 100 units/mL in the infusion fluids 0.9% sodium chloride, 5% dextrose with 40mEq potassium chloride and 0,45% sodium chloride or 10% dextrose using polyvinyl chloride infusion bags, are stable at room temperature for 24 hours.

Although stable over time, a certain amount of insulin will be initially adsorbed to the material of the infusion bag.

Administration with a syringe
Trurapi vials are for use with insulin syringes with the corresponding unit scale (see 4.1 Dosing Considerations).

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 d does not respond to glucagon within 10-15 minutes. Upon regaining consciousness, administration of an oral carbohydrate is recommended for the patient in order to prevent relapse. Hypokalemia must be corrected appropriately.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

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

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients

Subcutaneous Injection	Solution for injection, 100 Units/mL	Hydrochloric acid, metacresol, phenol, polysorbate 20, sodium chloride, sodium hydroxide, water for injection, zinc chloride

Trurapi is available in:

- 3 mL cartridges – pack of 5 or 10 cartridges
- 10 mL vials - pack of 1 vial
- Trurapi SoloSTAR disposable pens - pack of 5 pre-filled pens

The Trurapi cartridges should only be used with the following pens:

- JuniorSTAR which delivers Trurapi in 0.5 unit dose increments
- AllStar PRO which delivers Trurapi in 1 unit dose increments.

These cartridges should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pens.

Description

Trurapi (insulin aspart injection) is a unique human recombinant insulin analogue of rDNA origin that rapidly lowers blood glucose. Trurapi 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 Trurapi reduces the tendency to form hexamers as observed with regular human insulin. Trurapi is therefore more rapidly absorbed from the subcutaneous layer compared to regular human insulin. Insulin aspart is produced by recombinant DNA technology utilising *Escherichia coli (E. coli)* as the production organism. The fermentation, isolation, conversion and purification of insulin aspart are equivalent to the procedures used for production of genetically engineered human insulin.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

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 Trurapi and other insulin products.

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

Trurapi 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 Trurapi should immediately be followed by a meal. As a result of the short duration of action of Trurapi, 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 edema. 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, information when the use of these drugs in combination with any insulin, including Trurapi, is contemplated.

Never Share a Trurapi SoloSTAR pen or a Sanofi Insulin Delivery Device between patients.

Trurapi SoloSTAR pen, cartridges or a Sanofi Insulin Delivery Device should never be shared between patients, even if the needle is changed. Sharing poses a risk for transmission of bloodborne pathogens.

Carcinogenesis and Mutagenesis
See PART II: SCIENTIFIC INFORMATION – 10 NON-CLINICAL TOXICOLOGY.

Driving and Operating Machinery
Due 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 Trurapi. Such reactions following treatment with insulin aspart are mostly mild and easily managed. While the frequency of hypoglycemia observed in insulin aspart 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 Trurapi. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.

Patients, whose blood glucose control is greatly improved, e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycemia, and should be advised accordingly. Usual warning symptoms may disappear in patients with long-standing diabetes. Hypoglycemia may occur if the insulin dose is too high in relation to the insulin requirement (see 8 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 hypoglycemia.

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 Trurapi, 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 8 ADVERSE REACTIONS).

Hepatic/Biliary/Pancreatic
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, Trurapi 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

Injection Site and Local allergic reactions:
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 Trurapi. Localized reactions and generalized myalgias have been reported with injected metacresol, which is an excipient in Trurapi.

Lipodystrophy and Cutaneous Amyloidosis
Subcutaneous administration of insulin products, including Trurapi, can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) or localized cutaneous amyloidosis (skin lumps).

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and localized 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 glycemic 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 hypoglycemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered (see 8 ADVERSE REACTIONS).

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 7 WARNINGS AND PRECAUTIONS, Sexual Function/Reproduction and Special Populations, Pregnant Women, 8 ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, Pregnancy clinical trials; and Part II, SCIENTIFIC INFORMATION, 14 CLINICAL TRIALS, type 1 diabetes.

Monitoring and Laboratory Tests
As with all insulin therapy, the need for regular blood glucose self-monitoring should be considered when using Trurapi 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 patients with normal renal function Cl_{cr}:> 99.8 mL min^{-1}). The degree of renal impairment does not affect the pharmacokinetics variable of insulin aspart. As with other insulins, Trurapi requirement may be reduced in patients with renal impairment. Trurapi requirement may need to be adjusted in patients with severe renal impairment.

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

Reproductive Health: Female and Male Potential

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.

7.1 Special Populations

7.1.1 Pregnant Women

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

In a clinical trial of 157 pregnant women with type 1 diabetes treated with 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 7 WARNINGS AND PRECAUTIONS, Immune; 8 ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, Pregnancy clinical trials; and Part II, SCIENTIFIC INFORMATION, 14 CLINICAL TRIALS, type 1 diabetes.

Trurapi 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, 8.2 Clinical Trial Adverse Reactions, Pregnancy clinical trials and Part II, SCIENTIFIC INFORMATION, 14 CLINICAL TRIALS, type 1 diabetes).

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

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

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 ± 4.7 mmol/L, respectively; p=0.009; dinner: 10.5 ± 4.4 mmol/L vs.11.6 ± 4.8 mmol/L, respectively; p=0.003. Furthermore, insulin aspart did not increase the risk of hypoglycemia and had a safety profile comparable to both regular human insulin and lispro.

7.1.4 Geriatrics

PK/PD study comparing insulin aspart with soluble human insulin was performed in 19 elderly patients with type 2 diabetes. The relative differences in the pharmacodynamic properties between insulin apart 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 10 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.

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

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

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

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

Smoking
The effect of smoking on the pharmacokinetics and pharmacodynamics of Trurapi 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.

8 ADVERSE REACTIONS

The adverse drug reaction profiles reported in clinical studies that compared Trurapi 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.

8.1 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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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): Anaphylactic Reactions:

Symptoms of generalised hypersensitivity may include generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic edema, 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): edema

Edema 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 cæsarean section (see also 7 WARNINGS AND PRECAUTIONS, Immune, and Sexual Functions/reproduction and Special populations; Pregnant Women; and Part II, SCIENTIFIC INFORMATION, 14 CLINICAL TRIALS, type 1 diabetes).

8.3 Less Common Clinical Trial Adverse Reactions

In addition, the following adverse events were reported at an incidence of <1% for 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 edema, 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 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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

9.3 Drug-Behavioural 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 40 kg/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 Trurapi (insulin aspart injection) 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 Trurapi to obtain optimal glycemic control.

Alcohol may intensify or reduce the hypoglycemic effect of insulin.

9.4 Drug-Drug Interactions

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

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

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

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

Octreotide/lanreotide may either increase or decrease insulin requirements.

To avoid the risk of developing new or worsening heart failure, the use of TZDs in combination therapy with Trurapi is not indicated (see 7 WARNINGS AND PRECAUTIONS).

9.5 Drug-Food Interactions

Please refer to 10 CLINICAL PHARMACOLOGY, Mechanism of Action and 4

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 5 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 7 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 **Error! Not a valid bookmark self-reference.**).
- Short-acting insulin should be combined with a longer-acting insulin to maintain adequate glucose control (see 4 **Error! Not a valid bookmark self-reference.**).
- Insulin products shall not be mixed with any other insulin unless clearly indicated and done under medical supervision (see 7 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 **Error! Not a valid bookmark self-reference.**).

DOSAGE AND ADMINISTRATION for interactions with food and timing of food consumption, respectively.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

Trurapi 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 Trurapi 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.

10.2 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.

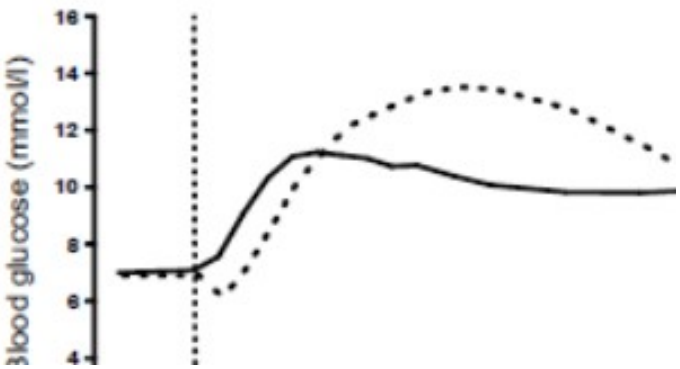


Figure 1: Mean blood glucose levels following a single pre-meal subcutaneous dose (0.15U/kg) of insulin aspart injected immediately before a meal (solid line) or regular human insulin administered 30 minutes before a meal (hatched line) in 22 patients with type 1 diabetes.

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.

10.3 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 Figure 1 and Figure 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.

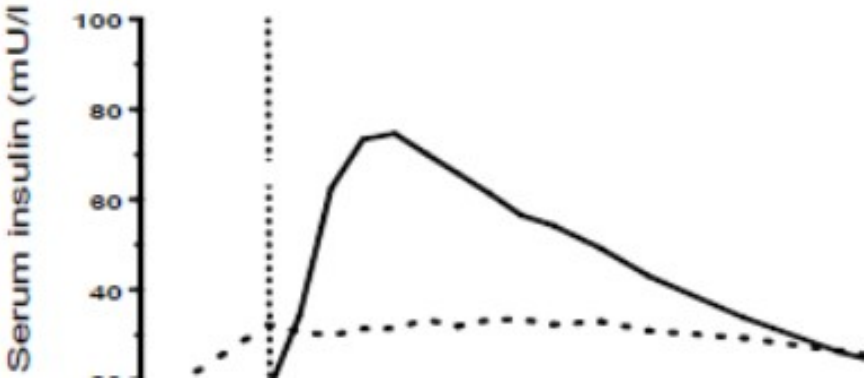


Figure 2: Mean serum insulin concentration following a single pre-meal subcutaneous dose (0.15 U/kg body weight) of insulin aspart injected immediately before a meal (solid line) or regular human insulin administered subcutaneously 30 minutes before a meal (hatched line) in 22 patients with type 1 diabetes.

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 (Figure 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 (Figure 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 72-126 mg/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.

Elimination
After subcutaneous administration insulin aspart was more rapidly eliminated than regular human insulin with an average apparent half-life of 81 minutes compared to 141 minutes for regular human

insulin. The rapid elimination of 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.

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

- **Hepatic Insufficiency**
  Some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. In an open-label, single-dose study of 24 patients with Child-Pugh Scores ranging from 0 (healthy volunteers) to 12 (severe hepatic impairment), no correlation was found between the degree of hepatic failure and any insulin aspart pharmacokinetic parameter. Careful glucose monitoring and dose adjustments of insulin, including Trurapi, may be necessary in patients with hepatic dysfunction (see 7 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 Trurapi, may be necessary in patients with renal dysfunction (see 7 WARNINGS AND PRECAUTIONS, Renal).

11 STORAGE, STABILITY AND DISPOSAL

Do not use after the expiration date.

Not in-use (unopened): Trurapi cartridges, Trurapi SoloSTAR and Trurapi vial should be stored in a refrigerator (2°C to 8°C) but not in the freezer. Do not use Trurapi if it has been frozen.

In-use (opened): Trurapi cartridges, Trurapi SoloSTAR and Trurapi vial should be stored at room temperature (15-30°C) and must be used within 4 weeks or be discarded, even if they still contain Trurapi. Protect from direct heat and light.

12 SPECIAL HANDLING INSTRUCTIONS

Inspect Trurapi before use. Trurapi must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of water-like consistency.

Inspect TRURAPI before use. TRURAPI must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of water-like consistency.

Trurapi which has been frozen must not be used.

Do NOT dilute or mix Trurapi when administering by continuous subcutaneous infusion.

Trurapi 100 units/mL solution for injection in vial
To prevent the possible transmission of disease, each vial must be used by one patient only, even if the needle is changed.

Trurapi vial may be used in an infusion pump system (CSII) subcutaneously as described in section 4.4 Administration. Tubings in which the inner surface materials are made of polyethylene have been evaluated and found compatible with pump use.

Trurapi vial may be used intravenously as described in section 4.4 Administration.

A new needle should always be used for each injection.

Syringes and needles are not included in the pack.

Patients must be instructed to carefully read the “SoloSTAR pre-filled pen Instructions for Use” and to use the pen as described in these Instructions for Use. If they do not follow all of these instructions, they may get too much or too little insulin.

The Trurapi cartridges should only be used with the following pens:
- JuniorSTAR which delivers Trurapi in 0.5 unit dose increments
- AllStar PRO which delivers Trurapi in 1 unit dose increments.

These cartridges should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pens. Patients should refer to the JuniorSTAR and AllStar PRO pen instructions for use leaflet supplied with the pens.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

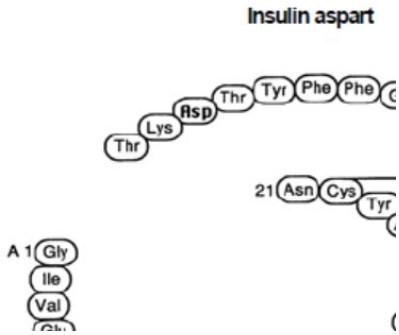
Drug Substance

Proper name: Insulin Aspart

Chemical name: 28B-L-Aspartic acid insulin (human). Recombinant human insulin analogue

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

Structural formula:



Physicochemical properties:

Description: white, or almost white, amorphous powder

Solubilities:

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

Absorption:

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

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

Product Characteristics:

Insulin aspart is produced by recombinant DNA technology utilising *Escherichia coli* as the production organism. The manufacture of the drug substance consists of the following three major steps: fermentation, recovery, and purification. In the recovery phase, the fermentation broth containing inactivated cells with inclusion bodies is harvested by continuous centrifugation.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

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

- PDY12695, a randomized study performed in Type 1 Diabetes Mellitus (T1DM) patients to demonstrate similarity in pharmacokinetic (PK) exposure and pharmacodynamic (PD) activity between Trurapi and NovoLog/NovoRapid.
- EFC15081 (GEMELLI-1), a randomized study performed in T1DM and Type 2 Diabetes Mellitus (T2DM) patients comparing the safety and efficacy of Trurapi and NovoRapid/NovoLog.

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 (M/F)
PDY12695	Phase 1, randomized, double-blind, controlled, 3-treatment, 3-period, 6-sequence crossover; active control *To compare exposure and activity of Trurapi to NovoRapid/NovoLog*	**Trurapi solution for injection:** or **NovoRapid/NovoLog:** – solution containing insulin aspart 100 U/mL single injection of 0.3 U/kg per period – subcutaneous **Duration:** 1 day in each period	30	44.0 ± 10.7 (22-59)	30/0

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 (M/F)
EFC15081	Phase 3, noninferiority, open-label, randomized (1:1), active-controlled, 2-arm, parallel-group study comparing: – Trurapi + Lantus with – NovoRapid/NovoLog + Lantus *in terms of change in HbA1c from baseline to Week 26 in patients with T1DM or T2DM*	**Trurapi solution for injection** or **NovoRapid/NovoLog** – solution containing insulin aspart 100 U/mL – injection 5 to 10 minutes before or immediately after each meal if allowed by the national product label for NovoLog/NovoRapid in order to achieve a 2-hour postprandial plasma glucose <10.0 mmol/L (<180 mg/dL) while avoiding hypoglycemia – subcutaneous **Duration:** 26 weeks	301 296 NovoLog (US) 165 NovoRapid (EU) 131	48.1 ± 15.1 (19-86)	356/241
PDY15083	Randomized, open-label, 2-treatment, 2-period, 2-sequence crossover Active control	**Trurapi solution for injection or NovoLog:** – solution containing insulin aspart 100 U/mL – dose titrated to achieve pre-prandial plasma glucose of 4.4 to 7.2 mmol/L and postprandial plasma glucose of <10.0 mmol/L – continuous subcutaneous infusion via insulin pump **Duration :** 4 weeks in each period	45	43.1 ± 13.6 (20-68)	17/28

14.2 Study Results

14.3 Comparative Bioavailability Studies

Pharmacokinetics

Table 3 - Comparative PK data for Trurapi versus reference product in patients with T1DM after single dose administration

Insulin aspart (0.3 U/kg) From measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test Trurapi**	**Reference NovoRapid***	**% Ratio of Geometric Means**	**90% Confidence interval (%)**
AUC_T (h.pg/mL)	13200 14000 (36.8)	14100 14800 (33.5)	92.7	88.4 to 97.3
AUC_I (h.pg/mL)	13100 13900 (36.3)	14300 15000 (33.4)	91.7	87.6 to 96.0
C_{max} (pg/mL)	5140 5320 (28.4)	5300 5490 (26.6)	97.2	90.0 to 104.9
t_{max} (h)[a]	1.17 (0.50 to 1.83)	1.17 (0.67 to 2.00)	-	-
$t_{1/2}$ (h)[b]	1.15 (126)	0.972 (35.2)	-	-

*NovoRapid: Manufacturer: NovoNordisk, country of origin: EU

[a] Median (Min to Max)

[b] Arithmetic Mean (CV%)

Evaluable profiles: N=29 for Test Trurapi, N=30 for Reference NovoRapid. Log-transformed AUC_{last}, AUC, and C_{max} were analysed with a linear mixed effects model, followed by anti-log-transformation of point estimates and confidence intervals.

Pharmacodynamics

Table 4 - Comparative PD data for Trurapi versus reference product in patient with T1DM after single dose administration

PARAMETER	**Test Trurapi**	**Reference NovoRapid***
GIR-$AUC_{0\text{-}12h}$ (mg/kg)		
Mean (SD)	1916.37 (524.28)	1966.71 (403.18)
Point estimate of treatment ratio (%) for Trurapi vs NovoRapid 95% confidence interval		96.2 (87.8 to 105.5)
GIR_{max} (mg/kg/min)		
Mean (SD)	9.34 (2.01)	9.23 (1.98)
Point estimate of treatment ratio (%) for Trurapi vs NovoRapid 95% confidence interval		101.8 (93.9 to 110.4)
GIR-t_{max} (h)		
Mean (SD)	2.41 (0.85)	2.70 (0.92)

Table 4 - Comparative PD data for Trurapi versus reference product in patient with T1DM after single dose administration

PARAMETER	Test Trurapi	Reference NovoRapid*
Point estimate of treatment difference for Trurapi vs NovoRapid		-0.29
95% confidence interval		(-0.68 to 0.02)

*NovoRapid: Manufacturer: NovoNordisk, country of origin: EU

Evaluable profiles: N=29 for Test Trurapi, N=30 for Reference NovoRapid

Log-transformed GIR-$AUC_{0\text{-}12h}$ and GIR_{max} were analysed with a linear mixed effects model, followed by anti-log-transformation of point estimates and confidence intervals. GIR-t_{max} was analysed by Hodges-Lehmann method with Moses confidence interval.

GIR_{max} and GIR-t_{max} are based on smoothed GIR profiles (LOESS smoothing technique with factor 0.06).

Comparative Safety and Efficacy

Efficacy

The efficacy and safety of Trurapi was compared to that of the reference product in a 26-week, open-label, randomized, active-controlled, 2-arm parallel-group study including 597 patients with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM).

The primary efficacy endpoint was the change in HbA1c from baseline to week 26 using a non-inferiority margin of 0.3%. The safety assessment included analysis of the immunogenicity of Trurapi and NovoLog/NovoRapid.

Patients with HbA1c in the range of 7% to 10% participated in this study comparing the glucose lowering effect of Trurapi to that of administration of the reference product, both in combination with insulin glargine 100 units/mL. Prior to randomization, 41.7%, 55.5% and 2.9% of the patients were taking the insulin lispro 100 units/mL, the reference product and both respectively. The patients were switched to Trurapi or reference product with a unit to unit conversion from the insulin lispro or reference product dose used prior to the trial or was a dose at the discretion of the investigator, taking into account the glucose control at the time of randomization. Trurapi or reference product was administered by subcutaneous injection immediately (within 5 to 10 minutes) prior to the start of a meal.

Among the 597 randomized patients, 497 had T1DM (83.2%) and 100 had T2DM (16.8%, US only). Mean age was 48 years, mean duration of diabetes was 19.5 years, 59.6% of patients were male, 82.6% were Caucasian, 3.2% were Black or African American, and 12.5% were Asian. The mean BMI was 27.45 kg/m^2 and 45.9% of patients had GFR≥90 mL/min/1.73 m^2.

At week 26, treatment with Trurapi provided a mean reduction in HbA1c that was non-inferior to that achieved with the reference product. Fasting plasma glucose decreased from baseline to week 26 in both treatment groups and no differences were observed in the percentage of patients achieving a target HbA1c <7%. The total daily doses of Trurapi and reference product, as well as the incidence of severe hypoglycemia were similar in the two treatment groups.

Table 5 - T1DM and T2DM adults (Trurapi plus insulin glargine 100 units/mL *versus* reference product plus insulin glargine 100 units/mL)

	Trurapi (n= 301)	Reference Product (n= 296)
Treatment duration	**26 weeks**	
HbA1c		
Baseline mean	8.00	7.94
Adjusted Mean change from Baseline	-0.38	-0.30
Adjusted mean difference [95% confidence interval]	-0.08 [-0.192 to 0.039]	
Proportion of patients achieving HbA1c<7%	16.6%	14.5%

Elderly

In a controlled clinical trial in adults (n=597, safety population), a total of 99 patients (16.5% of the safety population) with type 1 and type 2 diabetes patients were ≥65 years of age and 14 (2.3%) were ≥75 years of age. No difference in efficacy and safety was observed between these patients and younger patients.

Obesity

In a controlled clinical trial in adults (n=597, safety population), a total of 416 patients (69.7% of the safety population) with type 1 and type 2 diabetes patients had BMI <30 kg/m^2 and 181 (30.3%) had BMI ≥30 kg/m^2. Subgroup analysis based on BMI showed no differences in efficacy and safety between Trurapi and reference product.

Continuous Subcutaneous Insulin Infusion (CSII)

In a randomized, open-label crossover study in patients with type 1 diabetes (n=45) treated over two 4-week treatment periods, the incidence of infusion set occlusions in Trurapi treated patients and Novolog-treated patients was evaluated.

The results of the study do not suggest a clinically significant difference in the number of patients who had at least one infusion set occlusion with Trurapi (n = 14/43; 32.6%) and Novolog (n = 12/43; 27.9%) when used in CSII.

Safety

The types, frequency and severity of adverse events were comparable between the biosimilar and the reference biologic drug. The incidence of documented symptomatic hypoglycemia was similar [≤ 3.9 mmol/L: 87.7% Trurapi vs 84.8% reference; < 3.0 mmol/L: 68.4 Trurapi vs. 65.2% reference] in the two treatment groups. The incidence of severe hypoglycemia were similar [4% Trurapi vs 3.4% reference] in the two treatment groups. There was no episodes of diabetic ketoacidosis reported as SAEs in the reference product and 2 episodes in the Trurapi group.

14.4 Immunogenicity

Results from studies comparing Trurapi and reference product showed similarity in term of development of insulin aspart antibodies.

14.5 Clinical Trials - Reference Biologic Drug

Postprandial and overall glycemic control: In diabetic patients, NovoRapid® reduced postprandial

blood glucose levels and improved the overall glycemic control by significantly reducing A1C as shown in two 6-month multicentre, randomized, parallel, open-label trials. Metabolic control, assessed by A1C was studied in 882 type 1 diabetic patients in one trial and 1065 type 1 diabetic patients in another trial, on a meal-related insulin regimen. With NovoRapid®, significantly improved metabolic control was obtained compared to regular human insulin after 6 months treatment, the values being 7.78±0.03% for NovoRapid® 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 NovoRapid® was accompanied by a significant decrease of postprandial blood glucose levels after each meal, when compared to regular human insulin, without increasing the risk of hypoglycemic events.

Furthermore, NovoRapid® demonstrated a significant decrease in prandial blood glucose increments (defined as the mean difference between the blood glucose value 90 minutes after the meal and the blood glucose value just before the meal, over the 3 meals) when compared to regular human insulin; with values being -1.46mmol/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 NovoRapid® 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 NovoRapid® by continuous subcutaneous insulin infusion (CSII) with an external pump, one open-label, randomized, parallel design study for 16 weeks [n=118] compared NovoRapid® versus Humalog® (insulin lispro) in patients with type 1 diabetes. Glycemic control (as measured by A1C) and rates of hypoglycemia were comparable. Patients with type 2 diabetes were also studied in an open label, randomized, parallel design trial (24 weeks [n=127]. NovoRapid® by CSII was compared to a basal/bolus regimen of pre-prandial NovoRapid® and basal Novolin® ge NPH injections. Reductions in A1C and rates of hypoglycemia were comparable. In the study (NovoRapid® versus Humalog®), the rate of clogging or blockage events was similar between NovoRapid® and Humalog®.

Pregnancy

The safety and efficacy of an intensified insulin regimen with NovoRapid® was studied in an open-label study in 157 pregnant women with type 1 diabetes. 72% (113) were pregnant prior to entering the study (PBS) and 28% (44) entered the study before conception (PAS). The entry criteria for A1C were different between PBS and PAS (<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 NovoRapid® are presented in the following table.

Table 6 - 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 P4 (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.

Table 7 - All Treatment Emergent Hypoglycemic Episodes During Pregnancy by Treatment, pregnancy status at Screening and trimester - ITT Pregnant

		IAsp + NPH				
		P	N	%	E	Rate
Major	**Pregnant at Screening**					
	1. trimester	113	19	(16.80)	34	5.2
	2. trimester	113	22	(19.50)	44	1.3
	3. trimester	113	9	(8.00)	20	1
	Pregnant after Screening					
	1. trimester	44	5	(11.40)	7	0.8
	2. trimester	44	5	(11.40)	7	0.7
	3. trimester	44	1	(2.30)	1	0.2
	All					
	1. trimester	157	24	(15.30)	41	2.7

Table 7 - All Treatment Emergent Hypoglycemic Episodes During Pregnancy by Treatment, pregnancy status at Screening and trimester - ITT Pregnant

		IAsp + NPH				
		P	N	%	E	Rate
	2. trimester	157	27	(17.20)	51	1.2
	3. trimester	157	10	(6.40)	21	0.8
Minor	**Pregnant at Screening**					
	1. trimester	113	97	(85.80)	907	139.4
	2. trimester	113	98	(86.70)	2992	90.9
	3. trimester	113	85	(75.20)	1639	83.7
	Pregnant after Screening					
	1. trimester	44	40	(90.90)	607	69.3
	2. trimester	44	33	(75.00)	672	68.1
	3. trimester	44	27	(61.40)	380	67.4
	All					
	1. trimester	157	137	(87.30)	1514	98.9
	2. trimester	157	131	(83.40)	3664	85.7
	3. trimester	157	112	(71.30)	2019	80.1
Symptoms Only	**Pregnant at Screening**					
	1. trimester	113	32	(28.30)	154	23.5
	2. trimester	113	40	(35.40)	407	12.4
	3. trimester	113	34	(30.10)	256	13.1
	Pregnant after Screening					
	1. trimester	44	24	(54.50)	85	9.7
	2. trimester	44	15	(34.10)	118	12
	3. trimester	44	11	(25.00)	35	6.2
	All					
	1. trimester	157	56	(35.70)	39	15.6
	2. trimester	157	55	(35.00)	525	12.3
	3. trimester	157	45	(28.70)	291	11.5
Unclassifiable	**Pregnant at Screening**					
	1. trimester	113	4	(3.50)	11	1.7
	2. trimester	113	9	(8.00)	58	1.8
	3. trimester	113	6	(5.30)	34	1.7
	Pregnant after Screening					
	1. trimester	44	4	(9.10)	6	0.7
	2. trimester	44	4	(9.10)	6	0.6
	3. trimester	44	3	(6.80)	27	4.8

Table 7 - All Treatment Emergent Hypoglycemic Episodes During Pregnancy by Treatment, pregnancy status at Screening and trimester - ITT Pregnant

	IAsp + NPH				
	P	N	%	E	Rate

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

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

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 27.054.02, waist circumference 97.1±11.7 cm) was 20% lower following a single injection of NovoRapid® (injected immediately before a meal test) than regular human insulin (injected 30 minutes before a meal test; p=0.034), independent of BMI. The insulin maximum concentration (C_{max}) was significantly higher in patients receiving NovoRapid® (p=0.023) and was reached 27 minutes earlier (p=0.039), despite the fact that NovoRapid® was injected 30 minutes after human insulin.

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

Geriatrics: A randomised, double-blind, crossover trial compared the pharmacodynamics and pharmacokinetics of a single 0.3 U/kg s.c. dose of insulin apart (IAsp) and single 0.3 U/kg s.c. dose of soluble human insulin (HI) in 19 patients aged 65-83 years (mean age 70 years). IAsp was rapidly absorbed and the t_{max} for IAsp occurred 90 minutes earlier than for HI (p=0.0089). C_{max} was on average 132% higher with IAsp than with HI (p<0.0001). Also the extent of exposure with IAsp was greater than with HI up to approximately 300 minutes after administration but tended to be lower with IAsp than with HI from 300-600 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 euglycemic 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, NovoRapid® in combination with insulin detemir significantly improved glycemic control when compared to regular human insulin with NPH insulin treatment. After 18 weeks of treatment, the mean A1C values were 7.88±0.05% vs 8.11±0.05% (95% CI; -0.34 to -0.10, p<0.001), respectively. In addition, the overall mean postprandial plasma glucose was significantly lower with the combination NovoRapid®/detemir when compared to regular human

insulin/ NPH (7.81 mmol/L vs 7.87 mmol/L, respectively; p<0.001) with significant less intra-individual variability in plasma glucose (p<0.001). This improvement of glycemic control was accompanied with a significant decrease in the risk of nocturnal hypoglycemic events (relative risk decreased by 55%; 95% CI 0.35 - 0.58; p<0.001) and a significant decrease in body weight (p<0.001).

Hypoglycemia: In a 16-week double-blind, randomized, multinational, crossover study with type 1 diabetes patients (n=156, A1C ≤ 9.0%) the rate of major nocturnal hypoglycemic episodes was 72% lower with NovoRapid® than with regular human insulin {0.067 vs. 0.225 events/month, relative risk 0.28 (95% CI:0.13-0.59); p=0.001)}. NPH insulin was given as basal insulin once or twice daily as needed. Furthermore, NovoRapid® significantly reduced the rate of minor hypoglycemic events when with the rate of minor events was significantly reduced by 7% with NovoRapid® compared to regular human insulin {2.98 vs 3.186 events/months, relative risk 0.93 (95% CI:0.87-1.00), p=0.048}. While the total rate of major hypoglycemia did not differ significantly between treatments. Reductions in rate of hypoglycemia were achieved with NovoRapid® while maintaining overall glycemic control. The mean A1C remained constant, with values being 7.69% for NovoRapid® and 7.65% for regular human insulin (NS). Significant lower blood glucose values 90 minutes after breakfast (p=0.0001) and 90 minutes after dinner (p=0.023) were seen with NovoRapid® compared to regular human insulin.

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

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

16.1 Comparative Non-Clinical Pharmacology and Toxicology

The pharmacodynamic and toxicological responses to Trurapi (insulin aspart, also referred to as SAR341402) and reference insulin aspart (EU-NovoRapid and US-NovoLog) were compared in *in vitro* and *in vivo* studies.

16.1.1 Comparative Non-Clinical Pharmacodynamics

In vitro Studies

In *in vitro* pharmacodynamic studies, SAR341402 and reference insulin aspart demonstrated comparable binding affinities and binding kinetics with insulin receptors (IR-A and IR-B) and the IGF-1 receptor (IGF-1R). The biological activity (e.g. receptor activation of IR-A, IR-B, and IGF-1R), metabolic activity (e.g. inhibition of lipolysis, stimulation of glucose uptake, and gene regulation of glucose 6-phosphatase), and mitogenic potency of SAR341402 and insulin aspart were also comparable. No *in vivo* pharmacodynamic studies were conducted with SAR341402.

16.1.2 Comparative Toxicology

SAR341402 was tested in two, 1-month repeat-dose rat toxicity studies in comparison with insulin aspart NovoRapid or NovoLog at dose levels of 0, 5, 25, or 100 U/kg, administered by subcutaneous injection twice daily (corresponding to 10, 50, and 200 U/kg/day).

Administration of the SAR341402 versus insulin aspart resulted in a similar reduction in blood glucose levels within 1 to 4 hours of dosing, increase in body weight, and increase in food consumption. A total of 2 treatment-related premature deaths out of 168 treated animals occurred in one of the studies; the deaths were considered due to hypoglycemia. One animal was dosed with 50 U/kg/day insulin aspart, the other with 200 U/kg/day SAR341402. Hypoglycemia, increased body weight, and increased food consumption were considered indirect pharmacological reactions to the administration of insulin.

Anti-drug antibodies developed in a higher percentage of animals administered SAR341402 than those receiving the corresponding dose of insulin aspart. Overall, no toxicity or tolerability concerns were reported for SAR341402 that differed from those for reference insulin aspart.

A single-dose local tolerance study in New Zealand white male rabbits demonstrated similarity between SAR341402 and insulin aspart at a dose of 10 U by subcutaneous injection.

The macroscopic and microscopic findings were attributed only to the administration procedure, without significant differences between insulin aspart solutions and 0.9% NaCl control. Consequently, SAR341402 was considered well-tolerated following subcutaneous administrations, without local irritation.

Overall, the non-clinical studies in rats and rabbits demonstrated similarity between SAR341402 and reference insulin aspart regarding pharmacological activity, toxicity profile and local tolerability.

Toxicology – reference biologic drug

Acute Toxicity
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.

Table 8 - 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

Table 8 - Results of Acute Toxicity Studies with Insulin Aspart

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

Long-term Toxicity:

Table 9 - Results of long-term toxicity studies with insulin aspart.

Species	Strain	Number of groups and size	Dosing Method	Duration (Weeks)	Dose level (U/kg/day)	Results
Rat	Sprague-Dawley	5 Groups 10M, 10F/group, main 9M, 9F/group, satellites 5M, 5F in groups 1, 4 & 5 reversibility assessment	SC	4 weeks + 4 week recovery in groups 1, 4 & 5	0, 5, 25, 100 + 100	Hypoglycemia, increased food consumption and weight gain. No unexpected observations.
Rat	Sprague-Dawley	4 Groups 10M, 10F	SC	4 weeks	0, 12.5, 50, 200	Hypoglycemia. No unexpected observations.
Rat	Mol: WIST	4 Groups 15M, 15F	SC	13 weeks	0, 12.5, 50, 200	Hypoglycemia, increased weight gain. No unexpected observations.
Rat	Sprague-Dawley	4 Groups 32M, 32F Satellites included	SC	52 weeks	**Top dose levels** 100 bid for 24 weeks, 50 bid weeks 25-26, 100 od weeks 27-37, 75 od from week 38-52. **Lower dose levels** 5 and 25U/kg/bid for 26 weeks 10 and 50 od for 27-52 weeks. Controls.	Hypoglycemia, increased food and water consumption and weight gain. Excess of mammary tumours in high dose females.

Table 9 - Results of long-term toxicity studies with insulin aspart.

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

Carcinogenicity:
Carcinogenicity trials have not been performed with NovoRapid® (insulin aspart). A series of repeated dose trials in animals (including 52 weeks dosing in rats and dogs) showed that none of the effects observed with NovoRapid® differed from those observed with regular human insulin. *In vitro* trials showed that the mitogenicity of NovoRapid® does not differ from that observed with regular human insulin. Animal trials on the mutagenic potential of NovoRapid® and regular human insulin did not show any difference between the two products.

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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. NovoRapid® Solution for Injection 100 Units/mL, submission control 211441, Product Monograph, Novo Nordisk Canada Inc. April 6, 2018.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

TRURAPI® Cartridges (pronounced) troo-RA-pee

Insulin aspart injection

Cartridges are for use ONLY with AllStar® PRO and JuniorSTAR® pens. Please refer to the JuniorSTAR and AllStar PRO pen instructions for use leaflet supplied with the pens.

Read this carefully before you start taking **TRURAPI** 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 **TRURAPI**.

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.

TRURAPI 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.

Serious Warnings and Precautions

- Hypoglycemia (low blood sugar) is the most common adverse effect of insulin, including TRURAPI.
- If hypoglycemia or hyperglycemic 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.
- TRURAPI 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 TRURAPI”)
- Never inject your insulin directly into a vein.
- TRURAPI should not be used if it is not water-clear and colourless.

What is TRURAPI used for?

- The treatment of patients with diabetes mellitus who require insulin for the control of hyperglycemia (high blood sugar).

How does TRURAPI work?

- TRURAPI is an insulin analogue used to treat diabetes.
- TRURAPI 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 TRURAPI should normally be taken in combination with intermediate-acting or long-acting insulin preparations.

What are the ingredients in TRURAPI?

Medicinal ingredients: Insulin aspart

Non-medicinal ingredients: Hydrochloric acid, metacresol, phenol, polysorbate 20, sodium chloride, sodium hydroxide, water for injection, zinc chloride

TRURAPI comes in the following dosage forms:

Solution for Injection, 100 Units/mL

Do not use TRURAPI if:

- You feel a hypoglycemic reaction (low blood sugar) coming on. (see "What are possible side effects from TRURAPI?" 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 TRURAPI?")
- The TRURAPI or Sanofi Insulin Delivery Device containing the cartridge/JuniorSTAR and AllStar PRO is dropped, damaged or crushed; there is a risk of leakage of insulin.
- The insulin has not been stored correctly or if it has been frozen. (see "How to store TRURAPI")
- The insulin does not appear water-clear and colourless.

Do not refill a TRURAPI cartridge.

TRURAPI cartridges are designed to be used with JuniorSTAR and AllStar PRO Insulin Delivery Devices.

As a precautionary measure, you should carry an extra pen, insulin cartridges and needles.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TRURAPI. 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.

Other warnings you should know about:

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

Thiazolidinediones (class of oral antidiabetic drugs) used together with insulin may increase risk of edema (fluid retention/swelling of the lower extremities) and heart failure. Inform your doctor as soon as possible if you experience localised swelling (edema) 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).

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

TRURAPI may cause skin changes at the injection site. The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to take TRURAPI). Contact your healthcare professional if you are currently injecting into a lumpy area 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 TRURAPI:

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 such as Aspirin® (used to relieve pain and lower fever)
- Anabolic steroids (such as testosterone)
- Sulfa antibiotics (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 TRURAPI:

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.

Use TRURAPI exactly as your healthcare provider tells you to. Your healthcare provider should tell you how much TRURAPI to use and when to use it.

- Check your insulin label each time you give your injection to make sure you are using the correct insulin;
- **Use the TRURAPI cartridge only with AllStar PRO and JuniorSTAR pens.**
- **Do not** make any dose changes unless your healthcare provider tells you to;
- TRURAPI is injected under your skin (subcutaneously). Inject it into the front of your thighs, upper arms, buttock or the front of your waist (abdomen);
- Injection sites within an injection area (abdomen, thigh, buttock or upper arm) must be rotated from one injection to the next. This will reduce the risk of skin shrinking or thickening or lumps at the site (see What are possible side effects from using TRURAPI);
- **Do not** use the exact same spot for each injection;
- **Do not** inject where the skin has pits, is thickened, or has lumps;
- **Do not** inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin;
- **Do not** inject TRURAPI into your vein (intravenously);
- **Keep TRURAPI and all medicines out of the reach of children.**

TRURAPI is a clear solution and looks like some long-acting insulins. Always check for the name of the insulin on your carton and your TRURAPI cartridge label when you pick it up from the pharmacy to make sure it is the same as what your doctor recommended.

CAREFULLY FOLLOW THE DIRECTIONS SUPPLIED BY YOUR HEALTH PROFESSIONAL ON THE CORRECT USE OF YOUR AllStar PRO and JuniorSTAR, TO:

- **HELP AVOID CONTAMINATION AND POSSIBLE INFECTION**
- **OBTAIN AN ACCURATE DOSE.**

✗ The TRURAPI cartridge is for single patient use. Do not share it with anyone including other family members. Do not use on multiple patients.

✓ Always perform a safety test.

✓ Always carry a spare cartridge and spare needles in case they got lost or stop working.

As with all insulins, if patients are blind or have poor eyesight and cannot read the dose counter on the pen, they should get help from a person with good eyesight who is trained to use the insulin device.

Do not re-use the needle. A new sterile needle must be attached before each injection. Re-use of needles may increase the risk of blocked needles which may cause inaccurate dose delivery. Using a new sterile needle for each injection also minimizes the risk of contamination and infection.

Using the cartridge in any other injection pen not suitable for the TRURAPI cartridge could lead to a mistake in dosing and cause medical problems for you, such as a blood glucose level that is too low or too high.

- **JuniorSTAR delivers TRURAPI in 0.5 unit dose increments.**
- **AllStar PRO delivers TRURAPI in 1 unit dose increments.**

Although rare, technical problems with the cartridge can occur which may prevent correct dosing. They include: broken, cracked or damaged cartridges, air bubbles or foam, and blocked needles. If technical problems occur or are suspected, contact the call center, your physician, pharmacist or nurse.

Injection Procedure

Preparing the TRURAPI Cartridge for Insertion into the injection pen

1. To avoid medication errors, check the cartridge label of the insulin before each insertion.
2. Inspect the insulin cartridge. TRURAPI should be a clear and colourless solution with no visible particles. Do not use it if you notice anything unusual in the appearance of the solution.
3. Make sure the insulin is at room temperature to minimize local irritation at the injection site.
4. Wash your hands.
5. Carefully follow the injection pen directions for loading the cartridge into the injection pen.

Injecting the Dose

1. Wash your hands.
2. Inspect the insulin. TRURAPI should be a clear and colourless solution with no visible particles. Do not use it if you notice anything unusual in the appearance of solution.
3. It is not necessary to shake or rotate the cartridge inserted into the injection pen before use.
4. Remove the protective cap.
5. Follow the injection pen directions for attaching and changing the needle.
6. Check the cartridge inserted into the injection pen for air bubbles. If bubbles are present, remove them as instructed in the injection pen directions.
7. **Follow the injection pen directions for performing the Safety Test or Priming.**
8. Set the injection pen to the correct TRURAPI dose as instructed in the injection pen directions.
9. To avoid tissue damage, injection sites can be rotated so that the same site is not used more than approximately once a month.
10. Cleanse the skin with alcohol where the injection is to be made.
11. Pinch and hold the skin and insert the needle attached to the injection pen as instructed by your doctor or diabetes educator.
12. To inject TRURAPI, follow the directions for the injection pen.
13. Slowly count to 10 before removing the needle from the injection site and gently apply pressure for several seconds. DO NOT RUB THE AREA.
14. Remove the needle from the injection pen immediately after each injection as instructed in the directions for the injection pen. Dispose of the needle appropriately. Do not reuse the needle.

Hypo- or hyperglycemia can result from injecting insulin in the wrong site or incorrectly. Hypoglycemia can result from injection directly into a blood vessel and if not recognized or treated may be followed by hyperglycemia since there was no deposition for long-term absorption.

Usual dose:
Your doctor has told you which insulin to use, how much, and when and how often to inject it. Because each patient's case of diabetes is different, this schedule has been individualized for you.¸

Your usual TRURAPI dose may be affected by changes in your food, activity, or work schedule. Carefully follow your doctor's instructions to allow for these changes. Other things that may affect your TRURAPI dose are illness, pregnancy, medication, exercise and travel.

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

Overdose:
Hypoglycemia (too little glucose in the blood) is one of the most frequent adverse events experienced by insulin users. It can be brought about by:

1. Missing or delaying meals
2. Taking too much insulin
3. Exercising or working more than usual
4. An infection or illness (especially with diarrhea or vomiting)
5. A change in the body's need for insulin
6. Diseases of the adrenal, pituitary, or thyroid gland, or progression of kidney or liver disease
7. Interactions with other drugs that lower blood glucose, such as oral hypoglycemics, salicylates, sulfa antibiotics, and certain antidepressants
8. Consumption of alcoholic beverages

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.

Dietary Implications
If a usual meal cannot be obtained at the appropriate time, then to avoid hypoglycemia, you should take the amount of carbohydrate prescribed for this meal in the form of orange juice, syrup, candy, or bread and milk, without changing your insulin dosage. If it becomes necessary to omit a meal on account of nausea and vomiting, you should test your blood sugar level and notify your doctor.

Mild to moderate hypoglycemia may be treated by eating foods or drinks that contain sugar. Patients should always carry a quick source of sugar, such as candy mints or glucose tablets.

More severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious should be treated with intravenous administration of glucose at a medical facility or should be given an injection of glucagon (either intramuscular or subcutaneous). The patient should be given oral carbohydrates as soon as consciousness is recovered.

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.

If you think you, or a person you are caring for, have taken too much TRURAPI, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

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 TRURAPI?

These are not all the possible side effects you may have when taking TRURAPI. If you experience any side effects not listed here, tell your healthcare professional.

Like all medicines, TRURAPI 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 TRURAPI?”.

Less commonly reported side effects (1 to 10 users in 1000)

Signs of allergy

Hives and rash may occur.

Seek medical advice immediately

- If the above signs of allergy appear or
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty breathing; have a rapid heartbeat; feel dizzy.

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

Vision problems

When you first start your insulin treatment it may disturb your vision, but the disturbance is usually temporary.

Skin changes at the injection site

If you inject yourself too often at the same site, fatty tissue under the skin at this injection site may shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (localized cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Changing the site with each injection reduces the risk of developing such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or Diabetes Nurse Educator because these reactions can become more severe, or they may change the absorption of your insulin at this site.

Swollen joints

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

Diabetic retinopathy (eye background changes)

If you have diabetic retinopathy and your blood glucose levels improve very fast, the retinopathy may get worse. Ask your doctor about this.

Rarely reported side effects (less than 1 user in 10,000)

Painful neuropathy (nerve related pain)

If your blood glucose levels improve very fast you may get nerve related pain. This is called acute painful neuropathy and is usually transient.

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 a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

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

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

- Prior to first use, TRURAPI insulin cartridges should be stored in a refrigerator between 2° and 8°C.
- Do not freeze.
- Do not expose to excessive heat or sunlight.
- The pen and cartridge of TRURAPI that you are currently using should not be refrigerated but should be kept as cool as possible (15-30°C) and away from direct heat and light.
- Do not use TRURAPI if it has been frozen.
- Cartridges in use, or not refrigerated, should be discarded after 28 days, even if they still contain TRURAPI.

Inspection of Cartridge:
TRURAPI should be clear and colourless. DO NOT USE a cartridge of TRURAPI if it appears cloudy, thickened, or slightly coloured, or if solid particles are visible. A cartridge that is not clear and colourless or that is cracked or broken should be returned to the place of purchase for exchange.

If you notice anything unusual in the appearance or effect of your insulin, consult your healthcare professional

DO NOT USE A CARTRIDGE OF TRURAPI AFTER THE EXPIRATION DATE STAMPED ON THE LABEL.

Dispose of used needles in a puncture-resistant container or as directed by your healthcare professional.

Dispose of used pens as instructed by your healthcare professional and without the needle attached. Keep out of reach and sight of children.

If you want more information about TRURAPI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.sanofi.ca, or by calling 1-888-852-6887.

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This leaflet was prepared by sanofi-aventis Canada Inc.

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PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

TRURAPI® SoloSTAR® (Pre-filled disposable pen) (pronounced) troo-RA-pee

Insulin aspart injection

Read this carefully before you start taking **TRURAPI** 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 **TRURAPI**.

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.

TRURAPI 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.

Serious Warnings and Precautions

- Hypoglycemia (low blood sugar) is the most common adverse effect of insulin, including TRURAPI.
- If hypoglycemia or hyperglycemic 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.
- TRURAPI 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 TRURAPI”)
- Never inject your insulin directly into a vein.
- TRURAPI should not be used if it is not water-clear and colourless.

What is TRURAPI used for?

- The treatment of patients with diabetes mellitus who require insulin for the control of hyperglycemia (high blood sugar).

How does TRURAPI work?

- TRURAPI is an insulin analogue used to treat diabetes.
- TRURAPI 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 TRURAPI should normally be taken in combination with intermediate-acting or long-acting insulin preparations.

What are the ingredients in TRURAPI?

Medicinal ingredients: Insulin aspart

Non-medicinal ingredients: Hydrochloric acid, metacresol, phenol, polysorbate 20, sodium chloride, sodium hydroxide, water for injection, zinc chloride

TRURAPI comes in the following dosage forms:

Solution for Injection, 100 Units/mL

Do not use TRURAPI if:

- You feel a hypoglycemic reaction (low blood sugar) coming on. (see "What are possible side effects from TRURAPI?" 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 TRURAPI?")
- The TRURAPI or Sanofi Insulin Delivery Device containing the cartridge/JuniorSTAR and AllStar PRO is dropped, damaged or crushed; there is a risk of leakage of insulin.
- The insulin has not been stored correctly or if it has been frozen. (see "How to store TRURAPI")
- The insulin does not appear water-clear and colourless.

As a precautionary measure, you should carry an extra TRURAPI SoloSTAR pen and needles in case the pen does not work.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TRURAPI. 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.

Other warnings you should know about:

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

Thiazolidinediones (class of oral antidiabetic drugs) used together with insulin may increase risk of edema (fluid retention/swelling of the lower extremities) and heart failure. Inform your doctor as soon as possible if you experience localised swelling (edema) 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).

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

TRURAPI may cause skin changes at the injection site. The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to take TRURAPI). Contact your healthcare professional if you are currently injecting into a lumpy area 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 TRURAPI:

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 such as Aspirin® (used to relieve pain and lower fever)
- Anabolic steroids (such as testosterone)
- Sulfa antibiotics (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 TRURAPI:

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.

Read the detailed Instructions for Use that come with your TRURAPI® SoloSTAR® disposable prefilled pen. Use TRURAPI exactly as your healthcare provider tells you to. Your healthcare provider should tell you how much TRURAPI to use and when to use it.

- Check your insulin label each time you give your injection to make sure you are using the correct insulin;
- TRURAPI comes in a SoloSTAR disposable prefilled pen that you must use to take your TRURAPI. The dose counter on your pen shows your dose of TRURAPI. Do not make any dose changes unless your healthcare provider tells you to;
- TRURAPI is injected under your skin (subcutaneously). Inject it into the front of your thighs, upper arms, buttock or the front of your waist (abdomen);
- Injection sites within an injection area (abdomen, thigh, buttock or upper arm) must be rotated from one injection to the next. This will reduce the risk of skin shrinking or thickening or lumps at the site (see What are possible side effects from using TRURAPI);
- **Do not** use the exact same spot for each injection;
- **Do not** inject where the skin has pits, is thickened, or has lumps;
- **Do not** inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin;
- **Do not** inject TRURAPI into your vein (intravenously);
- **Keep TRURAPI and all medicines out of the reach of children.**

TRURAPI is a clear solution and looks like some long-acting insulins. Always check for the name of the insulin on your carton and your TRURAPI SoloSTAR pen label when you pick it up from the pharmacy to make sure it is the same as what your doctor recommended.

CAREFULLY FOLLOW THE DIRECTIONS SUPPLIED BY YOUR HEALTH PROFESSIONAL ON THE CORRECT USE OF YOUR TRURAPI SoloSTAR PEN TO:

- **HELP AVOID CONTAMINATION AND POSSIBLE INFECTION**
- **OBTAIN AN ACCURATE DOSE**

× The injection pen is for single patient use. Do not share it with anyone including other family members. Do not use on multiple patients.
× Never use your pen if it is damaged or if you are not sure that it is working properly.
✓ Always perform a safety test.
✓ Always carry a spare pen and spare needles in case they got lost or stop working.

The dose counter of the pen shows the number of units of TRURAPI to be injected.

As with all insulins, if patients are blind or have poor eyesight and cannot read the dose counter on the pen, they should get help from a person with good eyesight who is trained to use the insulin device.

Do not re-use the needle. A new sterile needle must be attached before each injection. Re-use of needles may increase the risk of blocked needles which may cause inaccurate dose delivery. Using a new sterile needle for each injection also minimizes the risk of contamination and infection.

Carefully read the "TRURAPI SoloSTAR pre-filled pen Instructions for Use" included in the package and use the pen as described. If you do not follow all of these instructions, you may get too much or too little insulin.

Injection Procedure

1. Take the new pen out of the fridge at least 1 hour before you inject. Make sure the insulin is at room temperature to minimize local irritation at the injection site; cold insulin is more painful to inject.
2. Check the name and expiration date on the label of your pen. To avoid medication errors between TRURAPI and other insulins, check the label on your TRURAPI SoloSTAR **pen to make sure you have the correct insulin before every injection. Never use your** pen after the expiration date.
3. **Check that the insulin is clear.** TRURAPI should be a clear and colourless solution with no visible particles. Do not use the pen if you notice anything unusual in the appearance of the solution.
4. **Wash your hands**.
5. **It is not necessary to shake or rotate the TRURAPI SoloSTAR pen before use.**
6. **Always attach a new needle.** Follow the TRURAPI SoloSTAR Instructions for Use for attaching and changing the needle.
7. **Pull off the protective cap and set it aside for later.**
8. **Do a safety test.** Always do a safety test before each injection to ensure your pen and needle are working correctly and to make sure that you get the correct insulin dose.
   - You may see air bubbles in the insulin – this is normal, they will not harm you.
9. **Select the correct dose.** Follow the steps included in your TRURAPI SoloSTAR Instructions for Use to ensure the correct dose of TRURAPI is selected.
   - Never select a dose or press the injection button without a needle attached – this may damage your pen.

10. **Choose a place to inject – upper arms, stomach, buttock or thighs.** There is no relevant difference in absorption of TRURAPI between your abdominal, thigh, buttock or upper arm subcutaneous injection areas.
    - Injection sites within an injection area (abdomen, thigh, buttock or upper arm) MUST be rotated from one injection to the next.
11. **Cleanse the skin with alcohol where the injection is to be made.**
12. **Push the needle into your skin as shown by your health provider.** Do not touch the injection button yet.
13. **Place your thumb on the injection button – press all the way in and hold.** Do not press at an angle – your thumb could block the dose selector from turning.
14. **Keep the injection button held in and when you see "0" in the dose window, slowly count to 10.** This will make sure you get your full dose. DO NOT RUB THE AREA.
15. **Remove the needle immediately after each injection**. Follow the steps included in your TRURAPI SoloSTAR Instructions for Use – do not re-use the needle.
    - Always take care when handling needles – this is to prevent injury and cross-infection. Never put the inner needle cap back on.
16. **Dispose of your needle appropriately.** Throw away the used needle in a puncture-resistant container or as instructed by your health provider or local authority.
17. **Put the pen cap back on.** Do not put the pen back in the fridge.

Hypo- or hyperglycemia can result from injecting insulin in the wrong site or incorrectly. Hypoglycemia can result from injection directly into a blood vessel and if not recognized or treated may be followed by hyperglycemia since there was no deposition for long-term absorption.

Usual dose:
Your doctor has told you which insulin to use, how much, and when and how often to inject it. Because each patient's case of diabetes is different, this schedule has been individualized for you.

Your usual TRURAPI dose may be affected by changes in your food, activity, or work schedule. Carefully follow your doctor's instructions to allow for these changes. Other things that may affect your TRURAPI dose are illness, pregnancy, medication, exercise and travel.

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

Overdose:
Hypoglycemia (too little glucose in the blood) is one of the most frequent adverse events experienced by insulin users. It can be brought about by:

1. Missing or delaying meals
2. Taking too much insulin
3. Exercising or working more than usual
4. An infection or illness (especially with diarrhea or vomiting)
5. A change in the body's need for insulin
6. Diseases of the adrenal, pituitary, or thyroid gland, or progression of kidney or liver disease
7. Interactions with other drugs that lower blood glucose, such as oral hypoglycemics, salicylates, sulfa antibiotics, and certain antidepressants
8. Consumption of alcoholic beverages

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.

Dietary Implications

If a usual meal cannot be obtained at the appropriate time, then to avoid hypoglycemia, you should take the amount of carbohydrate prescribed for this meal in the form of orange juice, syrup, candy, or bread and milk, without changing your insulin dosage. If it becomes necessary to omit a meal on account of nausea and vomiting, you should test your blood sugar level and notify your doctor.

Mild to moderate hypoglycemia may be treated by eating foods or drinks that contain sugar. Patients should always carry a quick source of sugar, such as candy mints or glucose tablets.

More severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious should be treated with intravenous administration of glucose at a medical facility or should be given an injection of glucagon (either intramuscular or subcutaneous). The patient should be given oral carbohydrates as soon as consciousness is recovered.

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.

If you think you, or a person you are caring for, have taken too much TRURAPI, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

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 TRURAPI?

These are not all the possible side effects you may have when taking TRURAPI. If you experience any side effects not listed here, tell your healthcare professional.

Like all medicines, TRURAPI 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 TRURAPI?".

Less commonly reported side effects (1 to 10 users in 1000)

Signs of allergy

Hives and rash may occur.
Seek medical advice immediately

- If the above signs of allergy appear or
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty breathing; have a rapid heartbeat; feel dizzy.

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

Vision problems
When you first start your insulin treatment it may disturb your vision, but the disturbance is usually temporary.

Skin changes at the injection site
If you inject yourself too often at the same site, fatty tissue under the skin at this injection site may shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (localized cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Changing the site with each injection reduces the risk of developing such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or Diabetes Nurse Educator because these reactions can become more severe, or they may change the absorption of your insulin at this site.

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

Diabetic retinopathy (eye background changes)

If you have diabetic retinopathy and your blood glucose levels improve very fast, the retinopathy may get worse. Ask your doctor about this.

Rarely reported side effects (less than 1 user in 10,000)

Painful neuropathy (nerve related pain)
If your blood glucose levels improve very fast you may get nerve related pain. This is called acute painful neuropathy and is usually transient.

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 a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

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

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

- Prior to first use, TRURAPI SoloSTAR should be stored in a refrigerator between 2° and 8°C.
- Do not freeze.
- Do not expose to excessive heat or sunlight.
- The TRURAPI SoloSTAR pen that you are currently using should not be refrigerated but should be kept as cool as possible (15-30°C) and away from direct heat and light.
- Do not use TRURAPI SoloSTAR if it has been frozen.
- Prefilled pens in use, or not refrigerated, should be discarded after 28 days, even if they still contain TRURAPI.

Inspection of the prefilled pen:
TRURAPI should be clear and colourless. DO NOT USE TRURAPI SoloSTAR if the solution appears cloudy, thickened, or slightly coloured, or if solid particles are visible. A prefilled pen cartridge that is not clear and colourless or that is cracked or broken should be returned to the place of purchase for exchange.

If you notice anything unusual in the appearance or effect of your insulin, consult your healthcare professional

DO NOT USE TRURAPI SoloSTAR AFTER THE EXPIRATION DATE STAMPED ON THE LABEL.

Dispose of used needles in a puncture-resistant container or as directed by your healthcare professional.

Dispose of used pens as instructed by your healthcare professional and without the needle attached.

Keep out of reach and sight of children.

If you want more information about TRURAPI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.sanofi.ca, or by calling 1-888-852-6887.

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This leaflet was prepared by sanofi-aventis Canada Inc.

Last Revised: July 20, 2022

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

TRURAPI® Vials (pronounced) troo-RA-pee

Insulin aspart injection

Read this carefully before you start taking **TRURAPI** 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 **TRURAPI**.

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.

TRURAPI 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.

Serious Warnings and Precautions

- Hypoglycemia (low blood sugar) is the most common adverse effect of insulin, including TRURAPI.
- If hypoglycemia or hyperglycemic 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.
- TRURAPI 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 TRURAPI”)
- Never inject your insulin directly into a vein.
- TRURAPI should not be used if it is not water-clear and colourless.

What is TRURAPI used for?

- The treatment of patients with diabetes mellitus who require insulin for the control of hyperglycemia (high blood sugar).

How does TRURAPI work?

- TRURAPI is an insulin analogue used to treat diabetes.
- TRURAPI 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 TRURAPI should normally be taken in combination with intermediate-acting or long-acting insulin preparations.
- Moreover TRURAPI can be used for continuous subcutaneous infusion in a pump system.

What are the ingredients in TRURAPI?

Medicinal ingredients: Insulin aspart

Non-medicinal ingredients: Hydrochloric acid, metacresol, phenol, polysorbate 20, sodium chloride, sodium hydroxide, water for injection, zinc chloride

TRURAPI comes in the following dosage forms:
Solution for Injection, 100 Units/mL

Do not use TRURAPI if:
- You feel a hypoglycemic reaction (low blood sugar) coming on. (see "What are possible side effects from TRURAPI?" 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 TRURAPI?")
- If the protective cap is loose or missing. Each vial has a protective, aluminium cap with tear-off lid. If it 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 TRURAPI")
- The insulin does not appear water-clear and colourless.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TRURAPI. 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 TRURAPI in other countries. If possible, bring enough TRURAPI with you on your trip.

Thiazolidinediones (class of oral antidiabetic drugs) used together with insulin may increase risk of edema (fluid retention/swelling of the lower extremities) and heart failure. Inform your doctor as soon as possible if you experience localised swelling (edema) 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).

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

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 TRURAPI:
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 such as Aspirin® (used to relieve pain and lower fever)
- Anabolic steroids (such as testosterone)
- Sulfa antibiotics (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 TRURAPI:
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.

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

Use TRURAPI exactly as your healthcare provider tells you to. Your healthcare provider should tell you how much TRURAPI to use and when to use it.

- Check your insulin label each time you give your injection to make sure you are using the correct insulin;
- **Do not** make any dose changes unless your healthcare provider tells you to;
- TRURAPI is injected under your skin (subcutaneously);
- Injection sites within an injection area (abdomen, thigh, buttock or upper arm) must be rotated from one injection to the next;
- **Do not** use the exact same spot for each injection;
- **Do not** inject TRURAPI into your vein (intravenously);
- **Keep TRURAPI and all medicines out of the reach of children.**

TRURAPI is a clear solution and looks like some long-acting insulins. Always check for the name of the insulin on your carton and your TRURAPI vial label when you pick it up from the pharmacy to make sure it is the same as what your doctor recommended.

CAREFULLY FOLLOW THE DIRECTIONS SUPPLIED BY YOUR HEALTH PROFESSIONAL ON THE CORRECT USE OF YOUR TRURAPI VIAL, TO:

- **HELP AVOID CONTAMINATION AND POSSIBLE INFECTION**
- **OBTAIN AN ACCURATE DOSE.**

✗ The TRURAPI vial is for single patient use. Do not share it with anyone including other family members. Do not use on multiple patients.

✓ Always use a new needle for each injection to prevent contamination.

✓ Needles and syringes must not be shared.

As with all insulins, if patients are blind or have poor eyesight and cannot read the syringe graduations, they should get help from a person with good eyesight who is trained to use the insulin device.

Do not re-use the needle. A new sterile needle must be attached before each injection. Re-use of needles may increase the risk of blocked needles which may cause inaccurate dose delivery. Using a new sterile needle for each injection also minimizes the risk of contamination and infection.

<u>Injection Procedure</u>

Trurapi vial containing insulin aspart

1 Draw into the syringe the same amount of air as the dose of insulin you are going to inject. Inject the air into the vial.

2 Turn the vial and syringe upside down and draw the correct insulin dose into the syringe. Pull the needle out of the vial. Then expel the air from the syringe and check that the dose is correct.

How to inject Trurapi

- Inject the insulin under the skin. Use the injection technique advised by your doctor or nurse.
- 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
Trurapi 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 Trurapi in a pump. Before use of Trurapi in the pump system, you must have received a comprehensive instruction in the 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 clean your hands and the skin where the needle is inserted 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 of 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 possible malfunction of the insulin pump, it is recommended that you measure your blood sugar level regularly.

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

Hypo- or hyperglycemia can result from injecting insulin in the wrong site or incorrectly. Hypoglycemia can result from injection directly into a blood vessel and if not recognized or treated may be followed by hyperglycemia since there was no deposition for long-term absorption.

Usual dose:
Your doctor has told you which insulin to use, how much, and when and how often to inject it. Because each patient's case of diabetes is different, this schedule has been individualized for you.

Your usual TRURAPI dose may be affected by changes in your food, activity, or work schedule. Carefully follow your doctor's instructions to allow for these changes. Other things that may affect your TRURAPI dose are illness, pregnancy, medication, exercise and travel.

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

Overdose:
Hypoglycemia (too little glucose in the blood) is one of the most frequent adverse events experienced by insulin users. It can be brought about by:

1. Missing or delaying meals
2. Taking too much insulin
3. Exercising or working more than usual
4. An infection or illness (especially with diarrhea or vomiting)
5. A change in the body's need for insulin
6. Diseases of the adrenal, pituitary, or thyroid gland, or progression of kidney or liver disease
7. Interactions with other drugs that lower blood glucose, such as oral hypoglycemics, salicylates, sulfa antibiotics, and certain antidepressants
8. Consumption of alcoholic beverages

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.

Dietary Implications:
If a usual meal cannot be obtained at the appropriate time, then to avoid hypoglycemia, you should take the amount of carbohydrate prescribed for this meal in the form of orange juice, syrup, candy, or bread and milk, without changing your insulin dosage. If it becomes necessary to omit a meal on account of nausea and vomiting, you should test your blood sugar level and notify your doctor.

Mild to moderate hypoglycemia may be treated by eating foods or drinks that contain sugar. Patients should always carry a quick source of sugar, such as candy mints or glucose tablets.

More severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious should be treated with intravenous administration of glucose at a medical facility or should be given an injection of glucagon (either intramuscular or subcutaneous). The patient should be given oral carbohydrates as soon as consciousness is recovered.

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.

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

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

Like all medicines, TRURAPI 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 TRURAPI?".

Less commonly reported side effects (1 to 10 users in 1000)

Signs of allergy
Hives and rash may occur.

Seek medical advice immediately
- If the above signs of allergy appear or
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty breathing; have a rapid heartbeat; feel dizzy.

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

Vision problems
When you first start your insulin treatment it may disturb your vision, but the disturbance is usually temporary.

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

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

This soon disappears.

Diabetic retinopathy (eye background changes)

If you have diabetic retinopathy and your blood glucose levels improve very fast, the retinopathy may get worse. Ask your doctor about this.

Rarely reported side effects (less than 1 user in 10,000)

Painful neuropathy (nerve related pain)

If your blood glucose levels improve very fast you may get nerve related pain. This is called acute painful neuropathy and is usually transient.

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 a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

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

- Visiting the Web page on Adverse Reaction Reporting (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:

- Prior to first use, TRURAPI insulin vials should be stored in a refrigerator between 2° and 8°C.
- Do not freeze.
- Do not expose to excessive heat or sunlight.
- Do not use TRURAPI if it has been frozen.
- Keep your TRURAPI vial that you are using at room temperature (below 30°C) for a maximum of 4 weeks. Do not keep the vial that you are using in the fridge or freeze. Keep the vial in the outer carton in order to protect from light.

Inspection of Vial:
TRURAPI should be clear and colourless. DO NOT USE a vial of TRURAPI if it appears cloudy, thickened, or slightly coloured, or if solid particles are visible. A vial that is not clear and colourless or that is cracked or broken should be returned to the place of purchase for exchange.

If you notice anything unusual in the appearance or effect of your insulin, consult your healthcare professional

DO NOT USE A VIAL OF TRURAPI AFTER THE EXPIRATION DATE STAMPED ON THE LABEL.

Dispose of used needles in a puncture-resistant container or as directed by your healthcare professional.

Keep out of reach and sight of children.

If you want more information about TRURAPI:

- 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 (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.sanofi.ca, or by calling 1-888-852-6887.

This leaflet was prepared by sanofi-aventis Canada Inc.

Last Revised: July 20, 2022

TRURAPI® SOLOSTAR® - INSTRUCTIONS FOR USE

Read this first

Important information

✗ Never share your pen – it is only for you.
✗ Never use your pen if it is damaged or if you are not sure that it is working properly.
✗ **Never use a syringe to remove insulin from your pen.**
✓ Always perform a safety test.
✓ Always carry a spare pen and spare needles in case they got lost or stop working.

Learn to inject

- Talk with your healthcare provider about how to inject, before using your pen.
- This pen is not recommended for use by people who are blind or have visual impairments without the assistance of a person trained in the proper use of the product.
- Read all of these instructions before using your pen. If you do not follow all of these instructions, you may get too much or too little insulin.

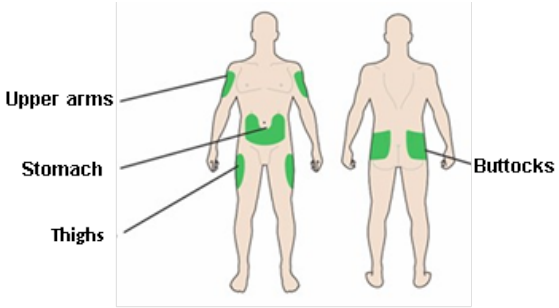
Need help?

If you have any questions about your pen or about diabetes, ask your healthcare provider, go to **www.sanofi.ca** or call sanofi-aventis at **1-888-852-6887.**

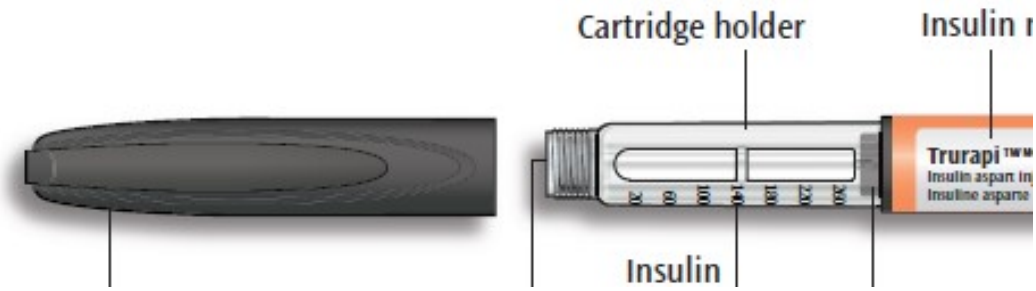
Extra items you will need:

- a new sterile needle (see STEP 2).
- an alcohol swab.
- a puncture resistant container for used needles and pens.

Places to inject



Get to know your pen



STEP 1: Check your pen

✓ Take a new pen out of the refrigerator at least 1 hour before you inject. Cold insulin is more painful to inject.

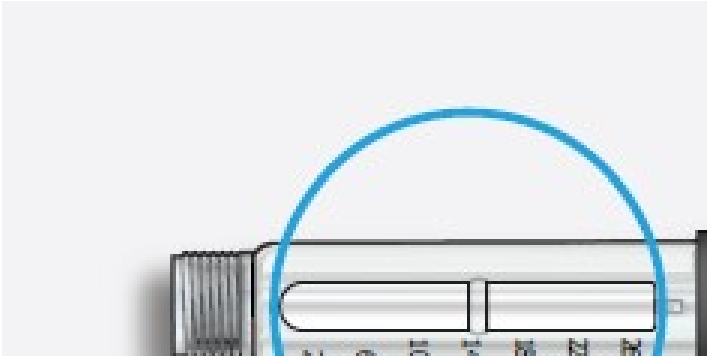
1A Check the name and expiration date on the label of your pen.

- Make sure you have the correct insulin.
- Never use your pen after the expiration date.

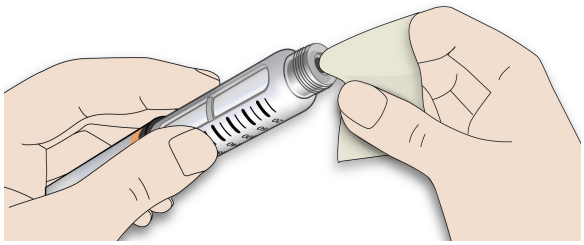
1B Pull off the pen cap.

1C Check that the insulin is clear.

- Do not use the pen if the insulin looks cloudy, coloured or contains particles.



1D Wipe the rubber seal with an alcohol swab.



ⓘ If you have other injector pens

- Making sure you have the correct medicine is especially important if you have other injector pens.

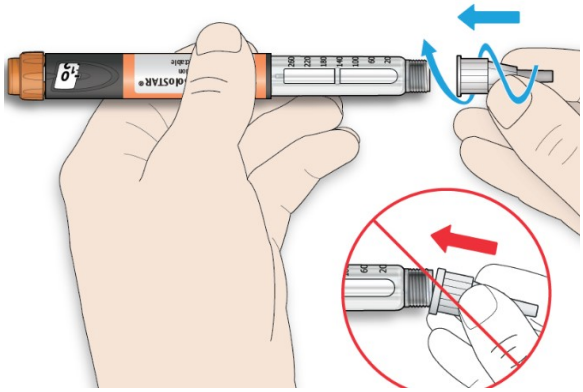
STEP 2: Attach a new needle

✓ Do not reuse needles. Always use a new sterile needle for each injection. This helps stop blocked needles, contamination and infection.

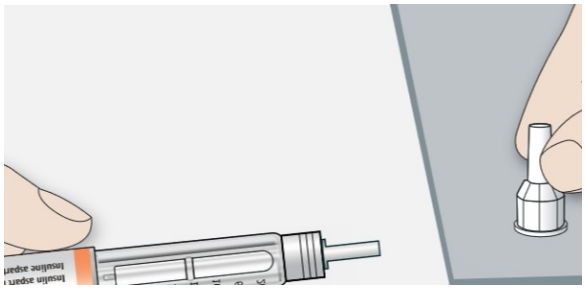
✓ Always use needles from Becton Dickinson (such as BD Ultra-Fine®), Ypsomed (such as Clickfine®) or Owen Mumford (such as Unifine® Pentips®)

2A Take a new needle and peel off the protective seal.

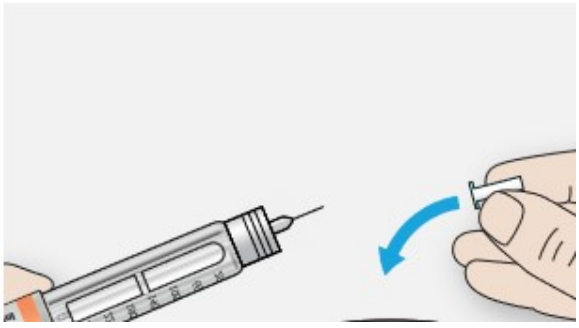
2B Keep the needle straight and screw it onto the pen until fixed. Do not overtighten.



2C Pull off the outer needle cap. Keep this for later.



2D Pull off the inner needle cap and throw away.



ⓘ Handling needles

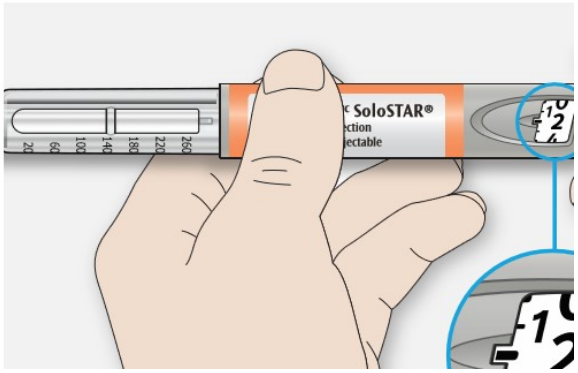
- Take care when handling needles – this is to prevent needle injury and cross-infection.

STEP 3: Do a safety test

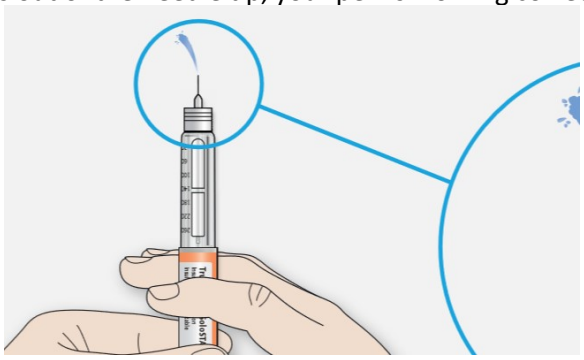
✓ Always do a safety test before each injection – this is to:
- Check your pen and the needle are working properly.
- Make sure that you get the correct insulin dose.

✓ **You must perform safety tests before you use the pen until you see insulin coming out of the needle tip. If you see insulin coming out of the needle tip, the pen is ready to use. If you do not see insulin coming out before taking your dose, you could get an underdose or no insulin at all. This could cause high blood sugar.**

3A Select 2 units by turning the dose selector until the dose pointer is at the 2 mark.



3B Press the injection button all the way in.
- When insulin comes out of the needle tip, your pen is working correctly.



3C Repeat this step if no insulin appears:
- **If you are using a new pen for the first time**, you may need to repeat this step **up to 3 times** before seeing insulin.
- **For all injections**, if no insulin comes out after the third time, the needle may be blocked. If this happens:
- change the needle (see STEP 6 and STEP 2),
- then repeat the safety test (STEP 3).
- Do not use your pen if there is still no insulin coming out of the needle tip. Use a new pen.
- Never use a syringe to remove insulin from your pen.

If you see air bubbles
- You may see air bubbles in the insulin. This is normal, they will not harm you.

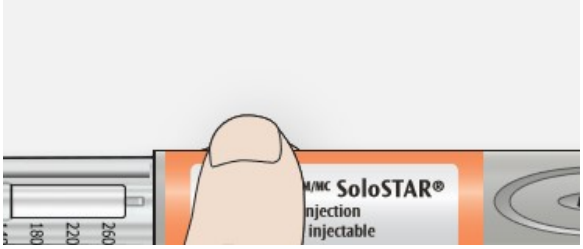
STEP 4: Select the dose

✗ Never select a dose or press the injection button without a needle attached. This may damage your pen.

4A Make sure a needle is attached and the dose is set to "0".

4B Turn the dose selector until the dose pointer lines up with your dose.

- Always check the number in the dose window to make sure you dialed the correct dose.
- If you turn past your dose, you can turn back down.
- If there are not enough units left in your pen for your dose, the dose selector will stop at the number of units left.
- If you cannot select your full prescribed dose, use a new pen or inject the remaining units and use a new pen to complete your dose. If you use a new pen, perform a safety test (see STEP 3).



How to read the dose window

Even numbers are shown in line with the dose pointer:

20 units selected

Odd numbers are shown as a line between even numbers:

21 units selected

Units of insulin in your pen

- Your pen contains a total of 300 units of insulin. You can select doses from 1 to 80 units in steps of 1 unit. Each pen contains more than one dose.
- You can see roughly how many units of insulin are left by looking at where the plunger is on the insulin scale.

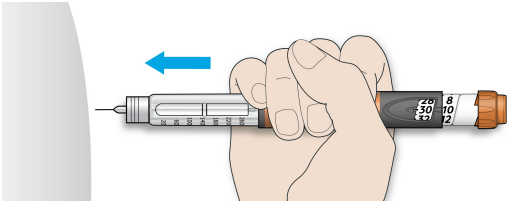
STEP 5: Inject your dose

✗ If you find it hard to press the injection button in, do not force it as this may break your pen. See the section below for help.

5A Choose a place to inject as shown in the picture labelled "Places to inject".

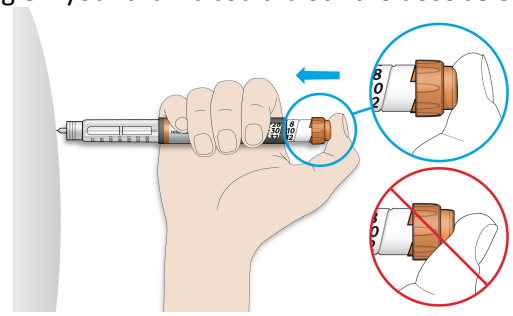
5B Push the needle into your skin as shown by your healthcare provider.

- Do not touch the injection button yet.



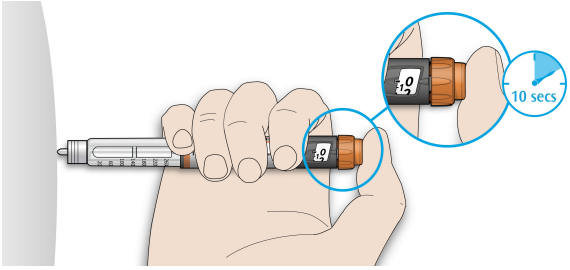
5C Place your thumb on the injection button. Then press all the way in and hold.

- Do not press at an angle – your thumb could block the dose selector from turning.



5D Keep the injection button held in and when you see "0" in the dose window, slowly count to 10.

- This will make sure you get your full dose.



5E After holding and slowly counting to 10, release the injection button. Then remove the needle from your skin.

If you find it hard to press the button in:

- Change the needle (see STEP 6 and STEP 2) then do a safety test (see STEP 3).
- If you still find it hard to press in, get a new pen.
- Never use a syringe to remove insulin from your pen.

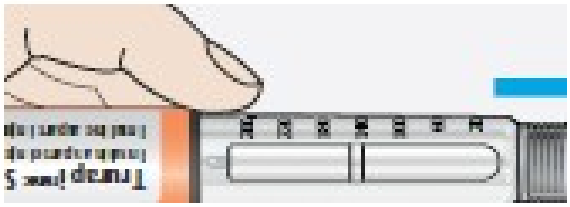
STEP 6: Remove the needle

✓ Take care when handling needles – this is to prevent needle injury and cross-infection.

✗ Never put the inner needle cap back on.

6A Grip the widest part of the outer needle cap. Keep the needle straight and guide it into the outer needle cap back
Then push firmly on.

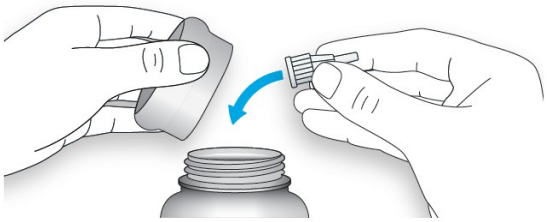
- The needle can puncture the cap if it is recapped at an angle.



6B Grip and squeeze the widest part of the outer needle cap. Turn your pen several times with your other hand to remove the needle.

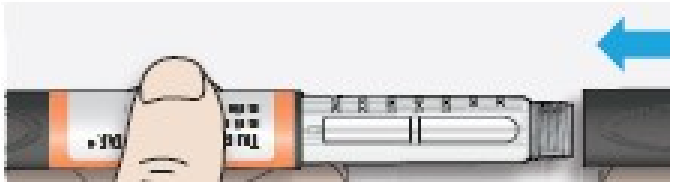
- Try again if the needle does not come off the first time.

6C Throw away the used needle in a puncture resistant container, or as told by your healthcare provider or local authority.



6D Put the pen cap back on.

- Do not put the pen back in the refrigerator.



Use by

- Only use your pen for up to 4 weeks after its first use.

How to store your pen

Before first use

- Keep new pens in a refrigerator at **2°C to 8°C**.
- Do not freeze.

After first use

- Keep your pen at room temperature (15-30°C)
- Never put your pen back in the refrigerator.
- Never store your pen with the needle attached.
- Store your pen with the pen cap on.
- Keep your pen away from heat or light.
- **Keep this pen out of the sight and reach of children.**

How to care for your pen

Handle your pen with care

- Do not drop your pen or knock it against hard surfaces.
- If you think that your pen may be damaged, do not try to fix it, use a new one.

Protect your pen from dust and dirt

- You can clean the outside of your pen by wiping it with a clean, damp cloth (water only). Do not soak, wash or lubricate your pen – this may damage it.

Throwing your pen away

- Remove the needle before throwing your pen away.
- Throw away your used pen as told by your healthcare provider or local authority.

Last Revised: July 20, 2022

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